yl)-1-piperidinecarboxylate (0.50 g, 11.26 mmol), 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (3.10 g, 12.39 mmol), sodium carbonate (2.90 g, 27.0 mmol) and tetrakis(triphenylphosphine)palladium (0.78 g, 0.67 mmol) in ethylene glycol dimethyl ether (90 mL) and water (45 mL) was heated at 85°C for 18 hours. The mixture was cooled and evaporated under reduced pressure then partitioned between water (50 mL) and dichloromethane (150 mL). The aqueous layer was extracted further with dichloromethane (2 X 50 mL) then the combined organic solutions were dried over magnesium sulfate and then filtered. The filtrate was concentrated and purified by flash chromatography on silica gel using dichloromethane/methanol (96:4) as an eluent to provide the title compound (4.51 g, 91%) as a tan solid: ^{1}H NMR (DMSO-d_6, 400MHz) δ 8.20 (s, 1H), 7.04 (s, 1H), 6.98 (d, 1H), 6.76 (d, 1H), 5.06 (bs, 1H), 4.86 (m, 1H), 4.08 (m, 2H), 3.83 (s, 3H), 2.90 (m, 2H), 2.03 (m, 2H), 1.90 (m, 2H), 1.43 (s, 9H); RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 25%-100% acetonitrile-0.05 M ammonium acetate over 10 min, 1 mL/min) t_r 9.70 min.

C. *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide acetate

A mixture of *tert*-butyl 4-[4-amino-3-(4-amino-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate (0.10 g, 0.228 mmol) in dichloromethane (2 mL) and pyridine (1 mL) was treated with 2-fluoro-4-trifluoromethylbenzoyl chloride (0.057 g, 0.251 mmol) then stirred for 1 hour. The solvents were evaporated then the residue was treated with trifluoroacetic acid (1 mL) in dichloromethane (2 mL). The mixture was stirred for 1 hour at ambient temperature then the solvents were evaporated under reduced pressure and the residue purified by RP preparative HPLC on a C18 column using acetonitrile-0.05 M ammonium acetate as a mobile phase. Lyophilization afforded the pure title compound: ^{1}H NMR (DMSO-d_6, 400MHz) δ 9.90 (d, 1H), 8.31 (d, 1H), 8.24 (s, 1H), 7.99 (t, 1H), 7.89 (d, 1H), 7.75 (d, 1H), 7.33 (s, 1H), 7.30 (d, 1H), 4.78 (m, 1H), 3.94 (s, 3H), 3.10 (m, 2H), 2.69 (m, 2H), 2.08 (m, 2H), 1.85-2.0 (m, 5H); RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 17.33 min;

MS:MH^+ 530.2.

Examples 636-710 were prepared from *tert*-butyl 4-[4-amino-3-(4-amino-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate and the appropriate acid chloride in a manner similar to that described for the preparation of *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide acetate (Example 635). In several cases functional group manipulation using standard organic chemistry techniques was required to obtain the desired compound. Free bases were obtained by partitioning the material obtained after preparative HPLC purification between aqueous sodium hydroxide and dichloromethane. The organic layer was dried over magnesium sulfate then filtered and the filtrate concentrated to provide the desired product.

Example 636: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-3-fluoro-4-(trifluoromethyl)benzamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 17.12 min; MS:MH^+ 530.2.

Example 637: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}benzamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 14.20 min; MS:MH^+ 444.1.

Example 638: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-3-phenylpropanamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 14.97 min; MS:MH^+ 472.2.

Example 639: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-3-cyclopentylpropanamide bisacetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 15.95 min; MS:MH^+ 464.2.

Example 640: *N*5-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1,3-dimethyl-1*H*-5-pyrazolecarboxamide bisacetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 11.62 min; MS:MH^+ 462.2.

Example 641: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-(2-thienyl)acetamide bisacetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 13.17 min; MS:MH^+ 464.2.

Example 642: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-phenylacetamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 13.63 min; MS:MH^+ 458.2.

Example 643: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-(3,4-dimethoxyphenyl)acetamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 13.20 min; MS:MH^+ 518.3.

Example 644: *N*1{-4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-

2-methoxyphenyl}-2-phenoxypropanamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 15.43 min; MS:MH^+ 488.2.

Example 645: *N*5-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-5-isoxazolecarboxamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 10.93 min; MS:MH^+ 433.1.

Example 646: *N*2-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-pyridinecarboxamide triacetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 13.52 min; MS:MH^+ 445.2.

Example 647: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2,4-difluorobenzamide bisacetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 14.65 min; MS:MH^+ 480.1.

Example 648: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2,5-difluorobenzamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 14.75 min; MS:MH^+ 480.2.

Example 649: *N*2-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-furamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm;

5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 13.40 min; MS:MH^+ 434.2.

Example 650: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2,2-dimethylpropanamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 14.53 min; MS:MH^+ 424.2.

Example 651: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-4-cyanobenzamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 13.68 min; MS:MH^+ 469.2.

Example 652: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-cyclopropanecarboxamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 11.05 min; MS:MH^+ 408.2.

Example 653: *N*3-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-methylnicotinamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 11.53 min; MS:MH^+ 459.1.

Example 654: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-4-fluoro-3-methylbenzamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 15.32 min; MS:MH^+ 476.2.

Example 655: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-3-(dimethylamino)benzamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 14.63 min; MS:MH^+ 487.2.

Example 656: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2,3-difluoro-4-methylbenzamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 16.03 min; MS:MH^+ 494.2.

Example 657: *N*4-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}isonicotinamide bisacetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 15.77 min; MS:MH^+ 445.1.

Example 658: *N*3-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}nicotinamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 17.50 min; MS:MH^+ 445.1.

Example 659: *N*2-{-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-pyrrolecarboxamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-50% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 22.20 min; MS:MH^+ 447.2.

Example 660: *N*3-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-

2-methoxyphenyl}-6-methylnicotinamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 17.97 min; MS:MH^+ 459.2.

Example 661: *N*2-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2- methoxyphenyl}-2-pyrazinecarboxamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 17.63 min; MS:MH^+ 446.1.

Example 662: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-4-iodobenzamide bisacetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 16.08 min; MS:MH^+ 570.1.

Example 663: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-4-bromobenzamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 15.42 min; MS:MH^+ 524.1.

Example 664: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-4-phenoxybenzamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 17.17 min; MS:MH^+ 536.2.

Example 665: *N*1-4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-4-fluorobenzamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm;

5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 13.65 min; MS:MH^+ 462.1.

Example 667: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-4-chlorobenzamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 15.57 min; MS:MH^+ 478.2.

Example 668: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-4-methoxybenzamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 13.62 min; MS:MH^+ 474.2.

Example 669: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-4-(trifluoromethoxy)benzamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 16.30 min; MS:MH^+ 528.2.

Example 670: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-4-nitrobenzamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 13.77 min; MS:MH^+ 489.2.

Example 671: *N*2-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}benzo[*b*]thiophene-2-carboxamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 16.12 min; MS:MH^+ 500.2.

Example 672: *N*2-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}benzo[*b*]furan-2-carboxamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 15.70 min; MS:MH^+ 484.2.

Example 673: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-4-methylbenzamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 15.47 min; MS:MH^+ 458.2.

Example 674: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-4-(*tert*-butyl)benzamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 17.93 min; MS:MH^+ 500.2.

Example 675: methyl 4-{(4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyanilino}carbonyl)benzoate acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 14.70 min; MS:MH^+ 502.1.

Example 676: 4-{(4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyanilino}carbonyl)benzoic acid

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 10.02 min; MS:MH^+ 478.1.

Example 677: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-

2-methoxyphenyl}-2-chlorobenzamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 25%-100% acetonitrile-0.05 M ammonium acetate over 10 min, 1 mL/min) t_r 7.28 min; MS:MH^+ 478.1.

Example 678: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-bromobenzamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 25%-100% acetonitrile-0.05 M ammonium acetate over 10 min, 1 mL/min) t_r 7.42 min; MS:MH^+ 524.1.

Example 679: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-methoxybenzamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 25%-100% acetonitrile-0.05 M ammonium acetate over 10 min, 1 mL/min) t_r 7.87 min; MS:MH^+ 474.2.

Example 680: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-phenylbenzamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 25%-100% acetonitrile-0.05 M ammonium acetate over 10 min, 1 mL/min) t_r 8.27 min; MS:MH^+ 520.2.

Example 681: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-(trifluoromethyl)benzamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 15.07 min; MS:MH^+ 512.2.

Example 682: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-(trifluoromethoxy)benzamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm;

5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 15.77 min; MS:MH^+ 528.2.

Example 683: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-3-methoxybenzamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 14.43 min; MS:MH^+ 474.2.

Example 684: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-3-(trifluoromethyl)benzamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 25%-100% acetonitrile-0.05 M ammonium acetate over 10 min, 1 mL/min) t_r 8.15 min; MS:MH^+ 512.2.

Example 685: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-3-(trifluoromethyl)benzamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 25%-100% acetonitrile-0.05 M ammonium acetate over 10 min, 1 mL/min) t_r 8.50 min; MS:MH^+ 530.2.

Example 686: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-6-(trifluoromethyl)benzamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 15.30 min; MS:MH^+ 530.2.

Example 687: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-5-(trifluoromethyl)benzamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 14.68 min; MS:MH^+ 530.2.

Example 688: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-5-methylbenzamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 13.32 min; MS:MH^+ 476.2.

Example 689: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-4-chloro-2-fluorobenzamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 16.50 min; MS:MH^+ 496.1.

Example 690: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-4-benzoylbenzamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 16.33 min; MS:MH^+ 548.2.

Example 691: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-4-acetylbenzamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 13.77 min; MS:MH^+ 486.2.

Example 692: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-4-isopropylbenzamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 17.10 min; MS:MH^+ 486.2.

Example 693: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-

2-methoxyphenyl}-4-ethylbenzamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 15.85 min; MS:MH^+ 472.2.

Example 694: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-4-propylbenzamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 17.02 min; MS:MH^+ 486.2.

Example 695: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-4-cyclohexylbenzamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 19.55 min; MS:MH^+ 526.2.

Example 696: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-4-ethoxybenzamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 15.28 min; MS:MH^+ 488.2.

Example 697: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-4-(methylsulfonyl)benzamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 13.01 min; MS:MH^+ 527.2.

Example 698: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-4-isopropoxybenzamide bisacetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm;

5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 16.20 min; MS:MH^+ 502.2.

Example 699: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-4-(1*H*-1-imidazolyl)benzamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 13.02 min; MS:MH^+ 510.2.

Example 700: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluorobenzamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 14.60 min; MS:MH^+ 462.3.

Example 701: *N*2-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-5-methoxybenzo[*b*]furan-2-carboxamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 15.38 min; MS:MH^+ 514.3.

Example 702: *N*2-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-5-bromobenzo[*b*]furan-2-carboxamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 17.03 min; MS:MH^+ 564.1.

Example 703: *N*2-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-5-methylbenzo[*b*]furan-2-carboxamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 16.27 min; MS:MH^+ 498.3.

Example 704: *N*2-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-3-methylbenzo[*b*]furan-2-carboxamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 16.67 min; MS:MH^+ 498.3.

Example 705: *N*2-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-5-nitrobenzo[*b*]furan-2-carboxamide

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 15.33 min; MS:MH^+ 529.2.

Example 706: *N*2-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-5-aminobenzo[*b*]furan-2-carboxamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 11.93 min; MS:MH^+ 499.3.

Example 707: *N*2-{4-[4-(acetylamino)-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-5-(acetylamino)benzo[*b*]furan-2- carboxamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 12.47 min; MS:MH^+ 583.2.

Example 708: *N*2-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-5-(acetylamino)benzo[*b*]furan-2-carboxamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 11.95 min; MS:MH^+ 541.2.

Example 709: *N*2-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-7-methylbenzo[*b*]furan-2-carboxamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 14.23 min; MS:MH^+ 498.3.

Example 710: *N*2-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-7-methoxybenzo[*b*]furan-2-carboxamide acetate

RP-HPLC (Hypersil HS C18 Hypersil HS C18, 5 μm, 100A, 250 X 4.6 mm; 5%-100% acetonitrile-0.05 M ammonium acetate over 25 min, 1 mL/min) t_r 13.03 min; MS:MH^+ 514.3.

Example 711: *rac-N*2-{4-[4-Amino-1-(1-methyltetrahydro-1*H*-3-pyrrolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}-5,7-dimethyl-1,3-benzoxazol-2-amine

A. *rac-tert*-butyl 3-hydroxy-1-pyrrolidinecarboxylate

To a solution of 3-pyrrolidinol (3.144 g, 3.00 mL, 36.09 mmol) in 1,4-dioxane (50 mL) and water (50 mL) was added di-*tert*-butyl dicarbonate (8.664 g, 39.70 mmol) and sodium bicarbonate (10.612 g, 126.3 mmol). The mixture was stirred at room temperature for 18 h to afford a white suspension in a yellow solution. The reaction mixture was filtered and the filtrate was extracted with ethyl acetate (2 x 50 mL). The combined organic phases were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated to afford *rac-tert*-butyl 3-hydroxy-1-pyrrolidinecarboxylate as a pale yellow oil (6.039 g, 89%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.51 (s, 9 H), 1.84-2.05 (m, 2 H), 2.28 (d, 1 H), 3.33-3.48 (m, 4 H), 4.43 (s, 1H).

B. *rac*-3-Iodo-1-tetrahydro-1*H*-3-pyrrolyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine monohydrochloride

To a solution of 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (5.610 g,

21.49 mmol) in tetrahydrofuran (200 mL) was added *rac-tert*-butyl 3-hydroxy-1-pyrrolidinecarboxylate (6.039 g, 32.25 mmol), triphenylphosphine (11.273 g, 42.98 mmol), and diethyl azodicarboxylate (7.485 g, 6.77 mL, 42.98 mmol). The reaction mixture was stirred at room temperature for 6 days and then concentrated to afford an orange-brown oil. Acetone (100 mL) and 5 N hydrochloric acid (50 mL) were added and the solution was heated at 40 °C for 18 h and then cooled to room temperature. The resulting yellow precipitate was filtered, and the filter cake was washed with diethyl ether and dried to afford *rac*-3-iodo-1-tetrahydro-1*H*-3-pyrrolyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine monohydrochloride as an off-white solid (5.153 g, 65%). RP-HPLC Rt 4.079 min, 99% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; $\lambda = 254$ nm; Deltapak C18, 300 Å, 5 μm, 150 x 3.9 mm column); *m/z* 331 (MH^+).

C. *rac*-3-Iodo-1-(1-methyltetrahydro-1*H*-3-pyrrolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

To a solution of *rac*-3-iodo-1-tetrahydro-1*H*-3-pyrrolyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine monohydrochloride (0.400 g, 1.09 mmol) in dichloroethane (10 mL) was added formaldehyde (37% in water, 0.12 mL, 1.63 mmol), sodium triacetoxyborohydride (0.578 g, 2.73 mmol), and acetic acid (0.37 mL, 6.55 mmol). The reaction mixture was stirred at room temperature for 3 days and then additional formaldehyde (37% in water, 0.12 mL, 1.63 mmol), sodium triacetoxyborohydride (0.578 g, 2.73 mmol), and acetic acid (0.37 mL, 6.55 mmol) were added. The reaction mixture stirred for an additional 3 h and was then concentrated to afford *rac*-3-iodo-1-(1-methyltetrahydro-1*H*-3-pyrrolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine as a pale yellow solid (0.639 g) which was used in subsequent reactions without further purification. RP-HPLC Rt 4.226 min, 96% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; $\lambda = 254$ nm; Deltapak C18, 300 Å, 5 μm, 150 x 3.9 mm column); *m/z* 345 (MH^+).

D. *N*2-(4-Bromophenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

1,1'-Thiocarbonyldi-2(1H)-pyridone (1.418 g, 6.104 mmol) was added to a solution of 4-bromoaniline (1.000 g, 5.813 mmol) in dichloromethane (50 mL). The

purple solution was stirred at room temperature for 30 min and then washed with water (50 mL) and 0.5 N hydrochloric acid (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated to afford a purple solid. 6-Amino-2,4-xylenol (0.837 g, 6.104 mmol) and toluene (50 mL) were added and the mixture was heated at 80 °C for 30 min. 1,3-Dicyclohexylcarbodiimide (1.799 g, 8.720 mmol) was added, and the solution was heated at 80 °C for 48 h and then cooled to room temperature. The resulting precipitate was filtered, and the filter cake was washed with dichloromethane (50 mL) to afford *N*2-(4-bromophenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine as a pale orange solid (1.215 g, 66%). RP-HPLC Rt 17.643 min, 86% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; $\lambda = 254$ nm; Deltapak C18, 300 Å, 5 μm, 150 x 3.9 mm column); *m/z* 317 (MH^+).

E. *N*2-[4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5,7-dimethyl-1,3-benzoxazol-2-amine

*N*2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5,7-dimethyl-1,3-benzoxazol-2-amine was prepared from *N*2-(4-bromophenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine (1.215 g, 3.831 mmol) in a manner similar to that used for the preparation of *N*2-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-benzoxazol-2-amine. The compound was formed as a tan powder (0.880 g, 63%). RP-HPLC (25 to 100 % CH_3CN in 0.1 N aqueous ammonium acetate over 10 min at 1 mL/min using a Hypersil HS C18, 250 x 4.6 mm column) Rt=14.48 min, 81%; *m/z* 365 (MH^+).

F. *rac*-*N*2-{4-[4-Amino-1-(1-methyltetrahydro-1*H*-3-pyrrolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}-5,7-dimethyl-1,3-benzoxazol-2-amine

rac-*N*2-{4-[4-Amino-1-(1-methyltetrahydro-1*H*-3-pyrrolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}-5,7-dimethyl-1,3-benzoxazol-2-amine was prepared from *rac*-3-iodo-1-(1-methyltetrahydro-1*H*-3-pyrrolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.200 g, 0.581 mmol) and *N*2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5,7-dimethyl-1,3-benzoxazol-2-amine (0.265 g, 0.726

mmol) in a manner similar to that used for the preparation of *cis*-*N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-fluorophenyl)-1,3-benzoxazol-2-amine. The compound was formed as a white powder (0.062 g, 23%). ^{1}H NMR (DMSO-d_6, 400 MHz) 2.39 (s, 3 H), 2.32-2.40 (m, 3 H), 2.40 (s, 3 H), 2.75-2.80 (m, 2 H), 3.08 (t, 1 H), 3.26 (s, 3 H), 5.40 (m, 1 H), 6.80 (s, 1 H), 7.11 (s, 1 H), 7.66 (d, 2 H), 7.93 (d, 2 H), 8.24 (s, 1 H), 10.85 (s, 1 H); RP-HPLC Rt 10.905 min, 96% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μm, 150 x 3.9 mm column); *m/z* 455 (MH^+).

Example 712: *rac*-*N*2-(4-{4-Amino-1-[1-(2-methoxyethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

A. *rac*-3-Iodo-1-[1-(2-methoxyethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

To a solution of *rac*-3-iodo-1-tetrahydro-1*H*-3-pyrrolyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine mono hydrochloride (0.350 g, 1.09 mmol) in N,N-dimethylformamide (10 mL) was added 2-bromoethylmethyl ether (0.159 g, 0.11 mL, 1.15 mmol), potassium carbonate (0.462 g, 3.34 mmol), and potassium iodide (0.008 g, 0.05 mmol). The reaction mixture stirred at 65 °C for 18 h and then additional 2-bromoethylmethyl ether (0.066 g, 0.040 mL, 0.48 mmol), potassium carbonate (0.130 g, 0.940 mmol), and potassium iodide (0.008 g, 0.05 mmol) were added. The reaction mixture was stirred for an additional 18 h and was then concentrated. The residue was partitioned between dichloromethane (10 mL) and water (10 mL). The organic phase was separated, washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated to afford *rac*-3-iodo-1-[1-(2-methoxyethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine as a yellow solid (0.313 g, 84%) which was used in subsequent reactions without further purification. RP-HPLC Rt 5.089 min, 80% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μm, 150 x 3.9 mm column); *m/z* 389 (MH^+).

B. *rac-N*2-(4-{4-Amino-1-[1-(2-methoxyethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

*rac-N*2-(4-{4-Amino-1-[1-(2-methoxyethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine was prepared from *rac*-3-iodo-1-[1-(2-methoxyethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.250 g, 0.515 mmol) and *N*2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5,7-dimethyl-1,3-benzoxazol-2-amine (0.235 g, 0.644 mmol) in a manner similar to that used for the preparation of *cis-N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-fluorophenyl)-1,3-benzoxazol-2-amine. The compound was formed as a yellow powder (0.185 g, 72%). ^{1}H NMR (DMSO-d_6, 400 MHz) 2.30-2.49 (m, 2 H), 2.41 (s, 3 H), 2.49 (s, 3 H), 2.66 (m, 2 H), 2.78 (m, 2 H), 3.17 (m. 2 H), 3.24 (s, 3 H), 3.45 (t, 2 H), 5.40 (m, 1 H), 6.80 (s, 1 H), 7.11 (s, 1 H), 7.66 (d, 2 H), 7.93 (d, 2 H), 8.24 (s, 1 H), 10.85 (s, 1 H); RP-HPLC Rt 11.477 min, 96% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μm, 150 x 3.9 mm column); *m/z* 499 (*MH*$^+$).

Example 713: *Cis-N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-fluorophenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

A. *N*2-(4-Bromo-2-fluorophenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

*N*2-(4-Bromo-2-fluorophenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine was prepared from 4-bromo-2-fluoroaniline (2.000 g, 10.53 mmol) in a manner similar to that usedfor the preparation of *N*2-(4-bromophenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine. The compound was formed as a pink solid (1.916 g, 54%). RP-HPLC Rt 17.96 min, 95% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μm, 150 x 3.9 mm column); *m/z* 337 (*MH*$^+$).

B. *N*2-[2-Fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5,7-dimethyl-1,3-benzoxazol-2-amine

*N*2-[2-Fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5,7-dimethyl-1,3-benzoxazol-2-amine was prepared from *N*2-(4-bromo-2-fluorophenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine (6.500 g, 19.39 mmol) in a manner similar to that used for the preparation of *N*2-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-benzoxazol-2-amine. The compound was formed as a pink solid (3.549 g, 48 %). RP-HPLC (25 to 100 % CH_3CN in 0.1 N aqueous ammonium acetate over 10 min at 1 mL/min using a Hypersil HS C18, 250 x 4.6 mm column) Rt=15.50 min, 78%; *m/z* 383 (MH^+).

C. *Cis-N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-fluorophenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

*Cis-N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-fluorophenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine was prepared from *cis*-3-iodo-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.200 g, 0.453 mmol) and *N*2-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5,7-dimethyl-1,3-benzoxazol-2-amine (0.216 g, 0.566 mmol) in a manner similar to that used for the preparation of *cis-N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-fluorophenyl)-1,3-benzoxazol-2-amine. The compound was formed as a pale yellow powder (0.111 g, 43%). ^{1}H NMR (DMSO-d_6, 400 MHz) 1.56-1.83 (m, 4 H), 2.15 (s, 3 H), 2.22-2.55 (m, 12 H), 2.34 (s, 3 H), 2.41 (s, 3 H), 3.22-3.53 (m, 1 H), 4.78-4.83 (m, 1 H), 6.81 (s, 1 H), 7.10 (s, 1 H), 7.45-7.53 (m, 2 H), 8.23 (s, 1 H), 8.49 (t, 1 H), 10.59 (s, 1 H); RP-HPLC Rt 11.873 min, 95% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μm, 150 x 3.9 mm column); *m/z* 570 (MH^+).

Example 714: *Cis*-3-(4-imidazo[1,2-*a*]pyridin-2-ylphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

A. 2-[4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]imidazo[1,2-*a*]pyridine

2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]imidazo[1,2-

a]pyridine was prepared from 2-(4-bromophenyl)imidazo[1,2-*a*]pyridine (0.273 g, 1.00 mmol) in a manner similar to that used for the preparation of *N*2-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-benzoxazol-2-amine. The compound was formed as a white solid (0.250 g, 78 %). RP-HPLC (25 to 100 % CH_3CN in 0.1 N aqueous ammonium acetate over 10 min at 1 mL/min using a Hypersil HS C18, 250 x 4.6 mm column) Rt=11.35 min, 87%; *m/z* 321 (MH^+).

B. *Cis*-3-(4-imidazo[1,2-*a*]pyridin-2-ylphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

Cis-3-(4-imidazo[1,2-*a*]pyridin-2-ylphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine was prepared from *cis*-3-iodo-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.200 g, 0.453 mmol) and 2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]imidazo[1,2-*a*]pyridine (0.250 g, 0.679 mmol) in a manner similar to that used for the preparation of *cis*-*N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-fluorophenyl)-1,3-benzoxazol-2-amine. The compound was formed as a white powder (0.021 g, 9%). ^{1}H NMR (DMSO-d_6, 400 MHz) 1.57-1.73 (m, 4 H), 2.08-2.50 (m, 12 H), 2.16 (s, 3 H), 3.37 (m, 1 H), 4.82 (m, 1 H), 6.92 (t, 1 H), 7.27 (t, 1 H), 7.61 (d, 1 H), 7.74 (d, 2 H), 8.15 (d, 2 H), 8.24 (s, 1 H), 8.56 (d, 1 H); RP-HPLC Rt 8.16 min, 97% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μm, 150 x 3.9 mm column); *m/z* 508 (MH^+).

Example 715: *rac*-1-[3-(4-Amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)tetrahydro-1*H*-1-pyrrolyl]-2-(dimethylamino)-1-ethanone

A. *rac*-1-[3-(4-Amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)tetrahydro-1*H*-1-pyrrolyl]-2-(dimethylamino)-1-ethanone

To a solution of *rac*-3-iodo-1-tetrahydro-1*H*-3-pyrrolyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine monohydrochloride (0.367 g, 1.00 mmol) in dichloromethane (10 mL) was added 2-(dimethylamino)acetic acid (0.134 g, 1.30 mmol), 1-hydroxy-

7-azabenzotriazole (0.150 g, 1.10 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.249 g, 1.30 mmol), and diisopropylethyl amine (0.65 g, 0.87 mL, 5.0 mmol). The reaction mixture stirred at room temperature for 18 h and was then poured into water (10 mL). The organic phase was separated and washed with brine (10 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated to afford *rac*-1-[3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)tetrahydro-1*H*-1-pyrrolyl]-2-(dimethylamino)-1-ethanone as a yellow-orange solid (0.278 g, 67%) which was used in subsequent reactions without further purification. RP-HPLC Rt 4.881 min, 80% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; $\lambda = 254$ nm; Deltapak C18, 300 Å, 5 μm, 150 x 3.9 mm column); *m/z* 416 (MH^+).

B. *rac*-1-[3-(4-Amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)tetrahydro-1*H*-1-pyrrolyl]-2-(dimethylamino)-1-ethanone

rac-1-[3-(4-Amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)tetrahydro-1*H*-1-pyrrolyl]-2-(dimethylamino)-1-ethanone was prepared from *rac*-1-[3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)tetrahydro-1*H*-1-pyrrolyl]-2-(dimethylamino)-1-ethanone (0.278 g, 0.669 mmol) and *N*2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5,7-dimethyl-1,3-benzoxazol-2-amine (0.305 g, 0.837 mmol) in a manner similar to that used for the preparation of *cis*-*N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-fluorophenyl)-1,3-benzoxazol-2-amine. The compound was formed as a white powder (0.219g, 62%). ^{1}H NMR (DMSO-d_6, 400 MHz) 2.17 (s, 3 H), 2.23 (s, 3 H), 2.3-2.50 (m, 4 H), 2.34 (s, 3 H), 2.40 (s, 3 H), 2.99-4.26 (m, 4 H), 5.44-5.49 (m, 1 H), 6.80 (s, 1 H), 7.11 (s, 1 H), 7.65 (d, 2 H), 7.92 (d, 2 H), 8.26 (s, 1 H), 10.86 (s, 1 H); RP-HPLC Rt 10.765 min, 96% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; $\lambda = 254$ nm; Deltapak C18, 300 Å, 5 μm, 150 x 3.9 mm column); *m/z* 526 (MH^+).

Example 716: *rac*-1-[3-(4-Amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)tetrahydro-1*H*-

1-pyrrolyl]-2-methyl-2-(methylamino)-1-propanone

A. *rac*-9*H*-9-Fluorenylmethyl *N*-{2-[3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)tetrahydro-1*H*-1-pyrrolyl]-1,1-dimethyl-2-oxoethyl}-*N*-methylcarbamate

To a solution of *rac*-3-iodo-1-tetrahydro-1*H*-3-pyrrolyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine monohydrochloride (0.100 g, 0.273 mmol) in dichloromethane (5 mL) was added 2-[[(9*H*-9-fluorenylmethoxy)carbonyl](methyl)amino]-2-methylpropanoic acid (0.120 g, 0.354 mmol), 1-hydroxy-7-azabenzotriazole (0.041 g, 0.30 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.068 g, 0.35 mmol), and diisopropylethyl amine (0.18 g, 0.24 mL, 1.4 mmol). The reaction mixture was stirred at room temperature for 5 h and then poured into water (10 mL). The organic phase was separated and washed with brine (10 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated to afford *rac*-9*H*-9-fluorenylmethyl *N*-{2-[3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)tetrahydro-1*H*-1-pyrrolyl]-1,1-dimethyl-2-oxoethyl}-*N*-methylcarbamate as a yellow solid (0.223 g) which was used in subsequent reactions without further purification. RP-HPLC Rt 13.688 min, 63% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; $\lambda = 254$ nm; Deltapak C18, 300 Å, 5 μm, 150 x 3.9 mm column); *m/z* 652 (MH^+).

B. *rac*-1-[3-(4-Amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)tetrahydro-1*H*-1-pyrrolyl]-2-methyl-2-(methylamino)-1-propanone

To a solution of *rac*-9*H*-9-fluorenylmethyl *N*-{2-[3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)tetrahydro-1*H*-1-pyrrolyl]-1,1-dimethyl-2-oxoethyl}-*N*-methylcarbamate (0.178 g, 0.273 mmol) in ethylene glycol dimethyl ether (6 mL) and water (3 mL) was added *N*2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5,7-dimethyl-1,3-benzoxazol-2-amine (0.124 g, 0.341 mmol), tetrakis(triphenylphosphine) palladium (0) (0.016 g, 0.014 mmol), and sodium carbonate (0.072 g, 0.683 mmol). The solution was heated at 80 °C for 18 h, and then cooled to room temperature. The reaction mixture was partitioned between ethyl acetate (10 mL) and water (10 mL). The organic layer was separated and washed with brine (10 mL), dried over anhydrous magnesium sulfate, filtered, and

concentrated to afford *rac*-9*H*-9-fluorenylmethyl *N*-2-[3-(4-amino-3-4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)tetrahydro-1*H*-1-pyrrolyl]-1,1-dimethyl-2-oxoethyl-*N*-methylcarbamate as a pale brown oil (0.223 g), which was used in the next step without further purification.

A solution of *rac*-9*H*-9-fluorenylmethyl *N*-2-[3-(4-amino-3-4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)tetrahydro-1*H*-1-pyrrolyl]-1,1-dimethyl-2-oxoethyl-*N*-methylcarbamate (0.223 g)in N,N-dimethylformamide (4 mL) was treated with piperidine (0.8 mL), and the reaction mixture stirred at room temperature for 18 h. The green solution was partitioned between dichloromethane (10 mL) and water (10 mL). The organic phase was separated and washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated to afford a dark green oil. Purification by preparative RP-HPLC (25 to 100 % CH_3CN in 0.1 N aqueous ammonium acetate over 20 min at 21 mL/min using a 8 μm Hypersil HS C18, 250 x 21 mm column, Rt = 6.7-8.1 min) afforded *rac*-1-[3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)tetrahydro-1*H*-1-pyrrolyl]-2-methyl-2-(methylamino)-1-propanone as an off-white solid (0.085 g, 58%). ^{1}H NMR (DMSO-d_6, 400 MHz) Major rotamer: 1.20 (s, 6 H), 1.96 (s, 3 H), 2.3-2.50 (m, 3 H), 2.34 (s, 3 H), 2.40 (s, 3 H), 3.17-4.44 (m, 4 H), 5.42 (s, 1 H), 6.80 (s, 1 H), 7.11 (s, 1 H), 7.63 (d, 2 H), 7.91 (d, 2 H), 8.26 (s, 1 H), 10.85 (s, 1 H); Minor rotamer: 1.15 (s, 6 H), 2.15 (s, 3 H), 2.3-2.50 (m, 3 H), 2.34 (s, 3 H), 2.40 (s, 3 H), 3.17-4.44 (m, 4 H), 5.42 (s, 1 H), 6.80 (s, 1 H), 7.11 (s, 1 H), 7.63 (d, 2 H), 7.91 (d, 2 H), 8.26 (s, 1 H), 10.85 (s, 1 H); RP-HPLC Rt 10.994 min, 95% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μm, 150 x 3.9 mm column); *m/z* 540 (MH^+).

Example 717: *rac-N*2-[4-(4-Amino-1-tetrahydro-1*H*-3-pyrrolyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl]-5,7-dimethyl-1,3-benzoxazol-2-amine

A. *rac-tert*-Butyl 3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-pyrrolidinecarboxylate

A solution of *rac*-3-iodo-1-tetrahydro-1*H*-3-pyrrolyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine monohydrochloride (0.500 g, 1.36 mmol), sodium bicarbonate

(0.401 g, 4.77 mmol), and di-*tert*-butyl dicarbonate (0.327 g, 1.50 mmol) in 1,4-dioxane (8 mL) and water (8 mL) was stirred at room temperature for 3 h. The resulting off-white suspension was filtered, and the filter cake was washed with water (10 mL) and dried to afford rac-*tert*-butyl 3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-pyrrolidinecarboxylate as an off-white solid (0.412 g, 70%). RP-HPLC Rt 11.540 min, 100% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; $\lambda = 254$ nm; Deltapak C18, 300 Å, 5 μm, 150 x 3.9 mm column); *m/z* 431 (MH^+).

B. *rac-N*2-[4-(4-Amino-1-tetrahydro-1*H*-3-pyrrolyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl]-5,7-dimethyl-1,3-benzoxazol-2-amine

To a solution of *rac-tert*-butyl 3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-pyrrolidinecarboxylate (0.412 g, 0.958 mmol) in ethylene glycol dimethyl ether (6 mL) and water (3 mL) was added *N*2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5,7-dimethyl-1,3-benzoxazol-2-amine (0.436 g, 1.20 mmol), tetrakis(triphenylphosphine) palladium (0) (0.055 g, 0.048 mmol), and sodium carbonate (0.254 g, 2.39 mmol). The solution was heated at 80 °C for 18 h, and then cooled to room temperature. The reaction mixture was partitioned between ethyl acetate (10 mL) and water (10 mL). The organic layer was separated and washed with brine (10 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated to afford *rac-tert*-butyl 3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-pyrrolidinecarboxylate as an orange solid (1.029 g), which was used in the next step without further purification.

6 N Hydrochloric acid (10 mL) was added to a solution of *rac-tert*-butyl 3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-pyrrolidinecarboxylate (1.029 g) in acetone (10 mL) and the reaction mixture was stirred at 45 °C for 5 h. The reaction mixture was filtered, and the resulting opaque filtrate was concentrated to afford an orange solid. Purification by preparative RP-HPLC (25 to 100 % CH_3CN in 0.1 N aqueous ammonium acetate over 20 min at 21 mL/min using a 8 μm Hypersil HS C18, 250 x 21 mm column, tr = 6.2-7.5 min) afforded *rac-N*2-[4-(4-amino-1-tetrahydro-1*H*-3-pyrrolyl-1*H*-

pyrazolo[3,4-*d*]pyrimidin-3-yl)phenyl]-5,7-dimethyl-1,3-benzoxazol-2-amine as an off-white solid (0.148 g, 35%). ^{1}H NMR (DMSO-d_6, 400 MHz) 2.15-2.22 (m, 2 H), 2.40 (s, 3 H), 2.50 (s, 3 H), 2.93-4.04 (m, 5 H), 5.31 (m, 1 H), 6.79 (s, 1 H), 7.11 (s, 1 H), 7.66 (d, 2 H), 7.93 (d, 2 H), 8.24 (s, 1 H), 10.85 (s, 1 H); RP-HPLC Rt 10.603min, 99% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μm, 150 x 3.9 mm column); *m/z* 441 (MH^+).

Example 718: *Cis-N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-7-isopropyl-1,3-benzoxazol-2-amine diacetate

A. 2-Amino-6-isopropylphenol

A solution of 6-isopropyl-2-nitrophenol (3.000 g, 16.56 mmol) and sodium hydrosulfite (11.53 g, 66.23 mmol) in ethanol (180 mL) and water (90 mL) was stirred at 80 ° C for 20 h and then cooled to room temperature. The resulting orange solution was concentrated and then partitioned between dichloromethane (50 mL) and water (50 mL). The organic phase was separated and washed with brine (25 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated to afford 2-amino-6-isopropylphenol as an orange solid (1.792 g, 72 %). RP-HPLC Rt 8.171 min, 92% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 A, 5 μm, 150 x 3.9 mm column); *m/z* 150 ($M-H)^-$.

B. *N*2-(4-Bromophenyl)-7-isopropyl-1,3-benzoxazol-2-amine

A solution of 2-amino-6-isopropylphenol (0.354 g, 2.34 mmol) and 4-bromophenylisothiocyanate (0.500 g, 2.34 mmol) in tetrahydrofuran (35 mL) was stirred at room temperature for 3 h. Anhydrous copper (II) sulfate (3.361 g, 21.06 mmol), silica gel (3.361 g), and triethylamine (0.236 g, 0.33 mL, 2.34 mmol) were added, and the mixture stirred at room temperature for 18 h. The reaction mixture was filtered through a pad of Celite and the washed with diethyl ether (3 x 50mL). The filtrate was concentrated to afford a brown solid. The solid material was applied to silica gel and passed through a pad a silica gel along with ethyl acetate (3 x 50mL). The filtrate was concentrated to afford *N*2-(4-bromophenyl)-7-isopropyl-

1,3-benzoxazol-2-amine (0.702 g, 91 %). RP-HPLC Rt 18.066 min, 86% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μm, 150 x 3.9 mm column); *m/z* 333 (MH^+).

C. *N*2-[4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-7-isopropyl-1,3-benzoxazol-2-amine

*N*2-[4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-7-isopropyl-1,3-benzoxazol-2-amine was prepared from *N*2-(4-bromophenyl)-7-isopropyl-1,3-benzoxazol-2-amine (0.412 g, 1.24 mmol) in a manner similar to that used for the preparation of *N*2-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-benzoxazol-2-amine. The compound was formed as an off-white solid (0.346 g, 74 %). RP-HPLC Rt 18.964 min, 79% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μm, 150 x 3.9 mm column); *m/z* 379 (MH^+).

D. *Cis-N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-7-isopropyl-1,3-benzoxazol-2-amine diacetate

*Cis-N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-7-isopropyl-1,3-benzoxazol-2-amine diacetate was prepared from *cis*-3-iodo-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.250 g, 0.566 mmol) and *N*2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-7-isopropyl-1,3-benzoxazol-2-amine (0.339 g, 0.708 mmol) in a manner similar to that used for the preparation of *cis-N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-fluorophenyl)-1,3-benzoxazol-2-amine. The compound was formed as an off-white solid (0.205 g, 64%). ^{1}H NMR (DMSO-d_6, 400 MHz) 1.36 (d, 6 H), 1.56-2.50 (m, 16 H), 1.90 (6 H), 2.15 (s, 3 H), 3.23-3.28 (m, 2 H), 4.80 (m, 1 H), 7.04 (d, 1 H), 7.18 (t, 1 H), 7.34 (d, 1 H), 7.66 (d, 2 H), 7.96 (d, 2 H), 8.24 (s, 1 H); RP-HPLC Rt 12.508 min, 100% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 A, 5 μm, 150 x 3.9 mm column); *m/z* 566 (MH^+).

Example 719: *N*2-(4-{4-Amino-1-[(3*S*)-1-(2-methoxyethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine monoacetate

*N*2-(4-{4-Amino-1-[(3*S*)-1-(2-methoxyethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine monoacetate was prepared from (*R*)-(+)-3-pyrrolidinol in a manner analogous to that used for the preparation of *rac*-*N*2-(4-{4-amino-1-[1-(2-methoxyethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine. The compound was formed as a pink solid (0.103 g, 53%). ^{1}H NMR (DMSO-d_6, 400 MHz) 1.89 (s, 3 H), 2.28-2.31 (m, 2 H), 2.35 (s, 3 H), 2.40 (s, 3 H), 2.65 (t, 2 H), 2.73-2.87 (m, 2 H), 3.17 (t, 2 H), 3.24 (s, 3 H), 3.45 (t, 2 H), 5.37 (m, 1 H), 6.79 (s, 1 H), 7.11 (s, 1 H), 7.66 (d, 2 H), 7.93 (d, 2 H), 8.24 (s, 1 H), 10.59 (s, 2 H); RP-HPLC Rt 11.607 min, 95% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μm, 150 x 3.9 mm column); *m/z* 499 (MH^+).

Example 720: *rac*-*N*2-(4-{4-Amino-1-[1-(2-methoxyethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-ethyl-1,3-benzoxazol-2-amine monoacetate

rac-*N*2-(4-{4-Amino-1-[1-(2-methoxyethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-ethyl-1,3-benzoxazol-2-amine monoacetate was prepared from *rac*-3-iodo-1-[1-(2-methoxyethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.200 g, 0.319 mmol) and *N*2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5-ethyl-1,3-benzoxazol-2-amine (0.145 g, 0.399 mmol) in a manner similar to that used for the preparation of *cis*-*N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-fluorophenyl)-1,3-benzoxazol-2-amine. The compound was formed as a white solid (0.082 g, 52%). ^{1}H NMR (DMSO-d_6, 400 MHz) 1.23 (t, 3 H), 1.90 (s, 3 H), 2.33-3.47 (m, 10 H), 2.66 (q, 2 H), 3.25 (s, 3 H), 5.40 (m, 1 H), 6.99 (d, 1 H), 7.33 (s, 1 H), 7.40 (d, 1 H), 7.66 (d, 2 H), 7.93 (d, 2 H), 8.25 (s, 1 H), 10.81 (s, 1 H); RP-HPLC Rt 11.781 min, 93% purity (5% to 85% acetonitrile/0.1M

aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μm, 150 x 3.9 mm column); *m/z* 499 (MH^+).

Example 721: *rac-N*2-(4-{4-Amino-1-[1-(2-methoxyethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-methyl-1,3-benzoxazol-2-amine monoacetate

*rac-N*2-(4-{4-Amino-1-[1-(2-methoxyethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-ethyl-1,3-benzoxazol-2-amine monoacetate was prepared from *rac*-3-iodo-1-[1-(2-methoxyethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.200 g, 0.319 mmol) and *N*2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5-methyl-1,3-benzoxazol-2-amine (0.145 g, 0.399 mmol) in a manner similar to that used for the preparation of *cis-N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-fluorophenyl)-1,3-benzoxazol-2-amine. The compound was formed as an off-white solid (0.038 g, 16%). ^{1}H NMR (DMSO-d_6, 400 MHz) 1.91 (s, 3 H), 2.33 (m, 2 H), 2.39 (s, 3 H), 2.66 (m, 2 H), 2.75-2.83 (m, 3 H), 3.17 (t, 1 H), 3.29 (s, 3 H), 3.45 (t, 2 H), 5.37 (m, 1 H), 6.96 (d, 1 H), 7.30 (s, 1 H), 7.38 (d, 1 H), 7.67 (d, 2 H), 7.93 (d, 2 H), 8.24 (s, 1 H), 10.80 (s, 1 H); RP-HPLC Rt 10.756 min, 100% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μm, 150 x 3.9 mm column); *m/z* 485 (MH^+).

Example 722: *N*2-(4-{4-Amino-1-[(3*R*)-1-(2-methoxyethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine diacetate

*N*2-(4-{4-Amino-1-[(3*R*)-1-(2-methoxyethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine diacetate was prepared from (*S*)-(-)-3-pyrrolidinol in a manner analogous to that used for the preparation of *rac-N*2-(4-{4-amino-1-[1-(2-methoxyethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine. The compound was formed as an off-white solid (0.214 g, 39%). ^{1}H NMR (DMSO-d_6, 400 MHz) 1.89 (s, 6 H), 2.28-2.31 (m, 2 H), 2.35 (s, 3 H), 2.40 (s, 3 H), 2.65 (t, 2 H), 2.73-2.87 (m, 2 H), 3.17 (t, 2 H), 3.24 (s, 3 H), 3.45 (t, 2 H), 5.37 (m, 1

H), 6.79 (s, 1 H), 7.11 (s, 1 H), 7.66 (d, 2 H), 7.93 (d, 2 H), 8.24 (s, 1 H); RP-HPLC Rt 11.674 min, 97% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μm, 150 x 3.9 mm column); *m/z* 499 (MH^+).

Example 723: *Rac-N*2-(4-{4-Amino-1-[1-(2-methoxyethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-chloro-1,3-benzoxazol-2-amine monoacetate

*rac-N*2-(4-{4-Amino-1-[1-(2-methoxyethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5-chloro-1,3-benzoxazol-2-amine monoacetate was prepared from *rac*-3-iodo-1-[1-(2-methoxyethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.200 g, 0.319 mmol) and *N*2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-5-chloro-1,3-benzoxazol-2-amine (0.148 g, 0.399 mmol) in a manner similar to that used for the preparation of *cis-N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-fluorophenyl)-1,3-benzoxazol-2-amine. The compound was formed as an off-white solid (0.080 g, 50%). ^{1}H NMR (DMSO-d_6, 400 MHz) 1.91 (s, 3 H), 2.33 (m, 2 H), 2.66 (m, 2 H), 2.75-2.85 (m, 3 H), 3.17 (t, 1 H), 3.24 (s, 3 H), 3.45 (t, 2 H), 5.37 (m, 1 H), 7.18 (d, 1 H), 7.55 (d, 2 H), 7.68 (d, 2 H), 7.92 (d, 2 H), 8.24 (s, 1 H), 9.80 (s, 1 H); RP-HPLC Rt 11.337 min, 97% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μm, 150 x 3.9 mm column); *m/z* 505 (MH^+).

Example 724: *trans-N*1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-3-phenylpropanamide

A solution of *trans*-3-(4-amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.700 g, 1.6 mmol) in pyridine (11 mL) at 0°C was treated with hydrocinnamoyl chloride (0.324 g, 1.92 mmol). The reaction mixture was stirred at 0°C for 20 min and the ice bath was removed to stir at room temperature. The reaction was complete after 5.5 hours. Sodium hydroxide solution (1 N, 20 mL) was added and stirred for 30 minutes. The

organic layer was removed under reduced pressure. Dichloromethane (20 mL) was added, and the layers were partitioned. The aqueous layer was extracted with dichloromethane (80 mL). The combined organic layers were washed with water, dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude material was purified by flash chromatography on silica gel using a gradient of 5% methanol in dichloromethane to 50% methanol in dichloromethane on a 35 g ISCO silica gel column to give 0.569 g (63%) of *trans-N*1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-3-phenylpropanamide. *trans-N*1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-3-phenylpropanamide (0.569 g, 1 mmol) in warmed ethyl acetate was treated with a warmed solution of maleic acid (0.384 g, 3 mmol) in ethyl acetate. The formed precipitate was filtered under a nitrogen atmosphere and dried under high vacuum to give the tri maleate salt. ^{1}H NMR (d_6-DMSO) δ 9.238 (s, 1H), 8.2216 (s, 1H), 8.1991-8.1786 (d, 1H, J = 8.2 Hz), 7.3147-7.2664 (m, 4H), 7.2366-7.2330 (m, 1H), 7.2026-7.1732 (dd, 2H), 6.171 (s, 6H), 4.6649-4.6083 (m, 1H), 4.0948-4.0697 (m, 1H), 3.8916 (s, 3H), 3.1750-3.1632 (d, 2H, J = 4.72 Hz), 2.9364-2.8984 (m, 2H), 2.7885-2.7506 (m, 2H), 2.5290 (s, 2H), 2.3905-2.3231 (m, 4H), 2.1489 (s, 3H), 2.0549-1.9243 (m, 6H), 1.4821-1.4457 (m, 2H); LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3μm particle size, 33 x 4.6mm; 70 % 50 mM ammonium Acetate in Water to 95% Acetonitrile over 6 min, 0.8 to 0.5 mL/min) R_t 1.75 min (100%), M^+ 569.4.

Example 725: *trans*-N2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1H-2-indolecarboxamide

A suspension of *trans-N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide di-maleate (0.200 g, 0.242 mmol) in dichloromethane (15 mL) was treated with 1N sodium hydroxide solution. The reaction mixture was stirred for 1 h at room temperature. The layers were partitioned using an Empore extraction cartridge. The organic layer was removed by

blowing nitrogen over the top of the solvent to give 0.072 g (50%) of *trans*-*N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide. ^{1}H NMR (d_6-DMSO) δ 9.4355 (s, 1H), 8.2464 (s, 1H), 8.1241-8.1037 (d, 1H, *J* = 8.16 Hz), 7.7186-7.6987 (d, 1H, *J* = 7.96 Hz), 7.6005-7.5795 (d, 1H, *J* = 8.4 Hz), 7.3532-7.2795 (m, 4H), 7.1717-7.1343 (t, 1H), 4.6833 (m, 1H), 4.0560 (s, 3H), 3.9573 (s, 3H), 2.6704 (m, 6H), 2.4404 (m, 2H), 2.2953 (s, 6H), 2.1282-1.9889 (m, 5H), 1.5124 (m, 2H). The compound was directly used in the subsequent reaction without purificaction.

Example 726: *trans*-*N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide di-mesylate

A warmed solution of *trans*-*N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide (0.072 g, 0.12 mmol) in ethyl acetate (20 mL) was treated with methane sulfonic acid (0.012 g, 0.12 mmol). A precipitate slowly formed and was filtered under a nitrogen atmosphere to give 0.051 g of *trans*-*N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide di-mesylate. The melting range was determined to be 345.5 to 348.1°C. ^{1}H NMR (d_6-DMSO) δ 9.4353 (s, 1H), 8.2461 (s, 1H), 8.1239-8.1035 (d, 1H, *J* = 8.16 Hz), 7.7182-7.6985 (d, 1H, *J* = 7.88 Hz), 7.6004-7.5792 (d, 1H, *J* = 8.48 Hz), 7.3442-7.2794 (m, 4H), 7.1718-7.1349 (t, 1H), 4.6829 (m, 1H), 4.0396 (s, 3H), 3.9570 (s, 3H), 2.6703 (m, 6H), 2.5 (s, 3H), 2.2949 (s, 6H), 2.0891-2.9086 (m, 7 H), 1.5179 (m, 2H).

Example 727: 3-(4-Amino-3-methoxyphenyl)-1-(1-methyl-4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine

A. 3-Iodo-1-(1-methyl-4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine

3-Iodo-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (500 mg, 1.45 mmol), formaldehyde (30% solution in water, 0.16 mL, 1.60 mmol) and sodium

triacetoxyborohydride (430 mg, 2.03 mmol) were mixed in 1,2-dichloroethane (5 mL). The reaction mixture was stirred at room temperature for 4 hours. Saturated sodium bicarbonate solution was added to adjust the pH to about 8. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated to give 3-iodo-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (275 mg, 53%). ^{1}H NMR (DMSO-d_6) δ 1.85 (m, 2H), 2.09 (m, 4H), 2.22 (s, 3H), 2.88 (m, 2H), 4.75 (m, 1H), 8.19 (s, 1H), 8.32 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.): MH^+ 359.0, R_t=0.46min.

B. *tert*-Butyl *N*-{4-[4-amino-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}carbamate

3-Iodo-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (270 mg, 0.754 mmol), *tert*-butyl *N*-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (290 mg, 0.829 mmol), palladium tetrakistriphenyphosphine (52 mg, 0.045 mmol) and sodium carbonate (192 mg, 1.81 mmol) were mixed in ethylene glycol dimethyl ether (8 mL) and water (4 mL). The reaction mixture was heated at reflux overnight under nitrogen. Organic solvent was removed under reduced pressure and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with water then brine, dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash column chromatography using dichloromethane/methanol (90:10 to 70:30) as mobile phase to give *tert*-butyl *N*-{4-[4-amino-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}carbamate (250 mg, 73%). ^{1}H NMR (DMSO-d_6) δ 1.48 (s, 9H), 1.88 (m, 2H), 2.10 (m, 2H), 2.24 (m, 5H), 2.92 (m, 2H), 3.69 (s, 3H), 4.64 (m, 1H), 7.21 (m, 2H), 7.91 (d, J=8.16 Hz, 1H), 8.04 (s, 1H), 8.23 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.): MH^+=454.2, R_t=1.67 min.

C. 3-(4-Amino-3-methoxyphenyl)-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

A mixture of trifluoroacetic acid/dichloromethane (20:80, 7 mL) was added to a solution of *tert*-butyl *N*-{4-[4-amino-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}carbamate (240 mg, 0.529 mmol) in dichloromethane (4 mL) at 0°C. 15 minutes later, the ice-bath was removed and the reaction mixture was stirred at room temperature for 4 hours. The solvents were evaporated and the residue was dissolved in dichloromethane. Sodium hydroxide (1.0N) was added to adjust the pH to about 10. The layers were separated and the aqueous layer was extracted with dichloromethane four times. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated to give 3-(4-amino-3-methoxyphenyl)-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (178 mg, 95%). HPLC (Waters 486 - Column: delta pak, C18, 5 um, 300 Å, 150x3.9 mm. Eluents: 5% B/A to 95% B/A in 10 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 1.0 mL/min.) R_t=6.45 min.

Example 728: *N*1-{4-[4-Amino-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-*trans*-2-phenyl-1-cyclopropanecarboxamide

trans-2-Phenyl-1-cyclopropanecarbonyl chloride (31 mg, 0.170 mmol) in dichloromethane (0.3 mL) was added to a solution of 3-(4-amino-3-methoxyphenyl)-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (60 mg, 0.17 mmol) in pyridine (1.2 mL) at 0°C. After 5 minutes, the ice-water bath was removed and the reaction mixture was stirred at room temperature for 1 hours then, more *trans*-2-Phenyl-1-cyclopropanecarbonyl chloride (15 mg, 0.083 mmol) was added. After 2 hours, the solvent was evaporated and the residue was purified by flash column chromatography using dichloromethane/methanol (95:5 to 70:30) as mobile phase to give *N*1-{4-[4-Amino-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-*trans*-2-phenyl-1-cyclopropanecarboxamide (75 mg, 89%). ^{1}H NMR ($CDCl_3$) δ 1.42 (m, 1H), 1.77 (m, 1H), 1.85 (m, 1H), 2.03 (m, 1H), 2.24 (m, 2H), 2.37 (s, 3H), 2.46 (m, 2H), 2.62 (m, 1H), 3.05 (m, 2H), 3.96 (s, 3H), 4.77 (m, 1H), 5.69 (s, 2H), 7.24 (m, 7H), 8.11 (s, 1H), 8.35 (m, 1H), 8.45 (d, J=8.38 Hz, 1H).

LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.): MH^+=498.3, R_t=1.84 min.

Example 729: *N*1-{4-[4-amino-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-4-(trifluoromethyl)benzamide

4-(Trifluoromethyl)-1-benzenecarbonyl chloride (35 mg, 0.170 mmol) in dichloromethane (0.3 mL) was added to a solution of 3-(4-amino-3-methoxyphenyl)-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (60 mg, 0.17 mmol) in pyridine (1.2 mL) at 0°C. After 5 minutes, the ice-water bath was removed and the reaction mixture was stirred at room temperature for 1 hours then, more 4-(trifluoromethyl)-1-benzenecarbonyl chloride (18 mg, 0.086 mmol) was added. 2 hours later, the solvent was evaporated and the residue was purified by flash column chromatography using dichloromethane/methanol (95:5 to 70:30) as mobile phase to give *N*1-{4-[4-amino-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-4-(trifluoromethyl)benzamide (85 mg, 95%). ^{1}H NMR ($CDCl_3$) δ 2.10 (m, 2H), 2.37-2.59 (m, 7H), 3.15 (m, 2H), 4.02 (s, 3H), 4.83 (m, 1H), 5.68 (s, 2H), 7.34 (m, 2H), 7.80 (d, J=8.21 Hz, 2H), 8.04 (d, J=8.10 Hz, 2H), 8.38 (s, 1H), 8.67 (m, 2H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC-Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.): MH^+=526.3, R_t=1.93 min.

Example 730: *N*1-{4-[4-amino-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-4-(trifluoromethoxy)benzamide

4-(Trifluoromethoxy)-1-benzenecarbonyl chloride (38 mg, 0.170 mmol) in dichloromethane (0.3 mL) was added to a solution of 3-(4-amino-3-methoxyphenyl)-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (60 mg, 0.17 mmol) in pyridine (1.2 mL) at 0°C. After 5 minutes, the ice-water bath was removed and the reaction mixture was stirred at room temperature for 1 hours then, more 4-(trifluoromethyl)-1-benzenecarbonyl chloride (19 mg, 0.085 mmol) was added. After 2 hours, the solvent was evaporated and the residue was purified by flash

column chromatography using dichloromethane/methanol (95:5 to 70:30) as mobile phase to give *N*1-{4-[4-amino-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-4-(trifluoromethoxy)benzamide (70 mg, 76%). ^{1}H NMR ($CDCl_3$) δ 2.06 (d, J=11.79 Hz, 2H), 2.28 (m, 2H), 2.40 (s, 3H), 2.50 (m, 2H), 3.07 (d, J=10.8 Hz, 2H), 4.02 (s, 3H), 4.80 (m, 1H), 5.71 (s, 2H), 7.27 (m, 2H), 7.36 (d, J=8.20 Hz, 2H), 7.98 (d, J=6.20Hz, 2H), 8.37 (s, 1H), 8.59 (s, 1), 8.67 (d, J=8.55 Hz, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.): MH^+=542.3, R_t=1.98 min.

Example 731: *cis*-1-[4-(4-Methylpiperazino)cyclohexyl]-3-[4-(1,3-oxazol-5-yl)phenyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amine

A. 4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}benzaldehyde

cis-3-Methyl-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (3.0 g, 6.80 mmol), 4-formylphenylboronic acid (1.22 g, 8.16 mmol), palladium tetrakistriphenyphosphine (0.47 g, 0.41 mmol) and sodium carbonate (1.73 g, 16.31 mmol) were mixed with ethylene glycol dimethyl ether (70 mL) and water (35 mL). The reaction mixture was heated at reflux overnight under nitrogen. Organic solvent was removed under reduced pressure and the aqueous layer was filtered and washed with water. After drying on the lyophilizer, the residue was purified by flash column chromatography using dichloromethane/methanol (90:10 to 70:30) as mobile phase to give 4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}benzaldehyde (1.55 g, 54%). ^{1}H NMR (DMSO-d_6) δ 1.60 (m, 2H), 1.72 (m, 2H). 2.07 (m, 2H), 2.15 (s, 3H), 2.22-2.46 (m, 11H), 4.83 (m, 1H), 7.88 (d, J=8.13 Hz, 2H), 8.07 (d, J=8.10 Hz, 2H), 8.21 (s, 1H), 10.11 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.): MH^+=420.2, R_t=0.70 min.

B. *cis*-1-[4-(4-Methylpiperazino)cyclohexyl]-3-[4-(1,3-oxazol-5-yl)phenyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amine

Sodium methoxide (130 mg, 2.41 mmol) was added in portions to a mixture of 4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}benzaldehyde (300 mg, 0.715 mmol) in methanol (20 mL). After 5 minutes, (p-tolylsulfonyl)methyl isocyanide (tosmic) (167 mg, 0.858 mmol) was added in portions. The solution was heated at reflux for 5 hours. Water (10 mL) was added while it was still hot. After cooling on ice for 5 minutes, the solid was filtered and washed with a mixture of methanol/water (50/50, 2 mL) then dried. The filtrate was evaporated to remove organic solvent and the solid was collected and washed with water. The combined solid was first purified by flash column chromatography using dichloromethane/methanol (90:10 to 70:30) as mobile phase then re-crystallized twice from DMF to give *cis*-1-[4-(4-methylpiperazino)cyclohexyl]-3-[4-(1,3-oxazol-5-yl)phenyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amine (90 mg, 27%). ^{1}H NMR (DMSO-d_6) δ 1.61 (m, 2H), 1.71 (m, 2H), 2.10 (m, 2H), 2.15 (s, 3H), 2.44 (m, 11H), 4.82 (m, 1H), 7.78 (m, 3H), 7.79 (m, 2H), 8.24 (s, 1H), 8.51 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.): MH^+=459.2, R_t=0.72 min.

Example 733: *trans-N*1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-5-fluoro-2-methoxyphenyl)-2,2-dimethyl-3-phenylpropanamide

2,2-Dimethyl-3-phenylpropanoyl chloride (52 mg, 0.264 mmol) was added to a solution of *trans*-3-(4-amino-2-fluoro-5-methoxyphenyl)-1-[4-(4-methylpiperazino) cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (80 mg, 0.176 mmol) in pyridine (1.5 mL). After 5 hours, the solvent was evaporated and the residue was first purified by flash column chromatography chromatography using dichloromethane/methanol (95:5 to 85:15) as mobile phase then by preparatory LC/MS to give *trans-N*1-(4-{4-amino-1-[4-(4-methylpiperazino) cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-5-fluoro-2-methoxyphenyl)-2,2-dimethyl-3-phenylpropanamide (22 mg, 19%). ^{1}H NMR ($CDCl_3$-*d*) δ 1.33 (s, 6H), 1.57 (m,

2H), 1.92 (m, 2H), 2.15 (m, 6H), 2.30 (s, 3H), 2.49 (m, 4H), 2.66 (m, 3H), 2.95 (s, 2H), 3.84 (s, 3H), 4.76 (m, 1H), 5.51 (bs, 2H), 6.98 (d, J=6.86Hz, 1H), 7.15 (m, 2H), 7.23 (m, 3H), 8.01 (s, 1H), 8.35 (s, 1H), 8.47 (d, J=11.88, 1H). LCMS LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.): MH^+=615.3, R_t=2.18 min.

Example 734: *cis*-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)(1H-benzo[d]imidazol-2-yl)methanol

A. 1*H*-Benzo[d]imidazol-1-ylmethanol

Formaldehyde (37% in water, 1 mL, 13.3 mmol) was added to a solution of 1*H*-benzo[*d*]imidazole (1.57 g, 13.3 mmol) in THF (60 ml). After 10 minutes, the solvent was removed and dried to give 1*H*-benzo[*d*]imidazol-1-ylmethanol as a brown solid which was used without any further purification. ^{1}H NMR (DMSO-d_6) δ 5.60 (d, J=7.09Hz, 2H), 6.70 (m, 1H), 7.25 (m, 2H), 7.65 (d, J=9.13Hz, 2H), 8.26 (s, 1H).

B. *cis*-(4-{4-Amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)(1*H*-benzo[*d*]imidazol-2-yl)methanol

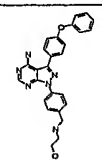
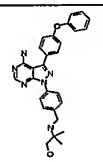
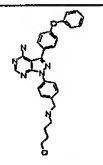
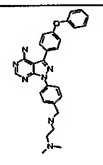
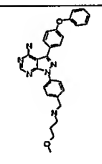
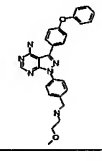
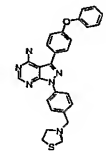
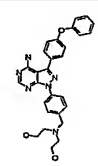
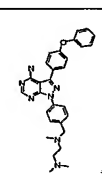
n-Butylithum (1.34M, 3.0 mL, 4 mmol) was added slowly to a mixture of 1*H*-benzo[*d*]imidazol-1-ylmethanol (296 mg, 2.0 mmol) in THF (9.0 mL) at –78°C. The reaction mixture was allowed to warm up to –20°C and kept at –20°C for 30 minutes then cooled back to –78°C. *cis*-4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}benzaldehyde (420 mg, 1 mmol) in THF (5 mL) was added slowly. After 20 minutes, the dry ice bath was removed and the reaction mixture was stirred at room temperature overnight. Saturated ammonium chloride solution was added followed by ether. The layers were separated and the aqueous layer was neutralized with sodium hydroxide (1.0N) and extracted with dichloromethane. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated. The residue was first purified by flash column chromatography using dichloromethane/methanol (95:5 to 85:15) as mobile phase then by reverse phase preparative HPLC (Rainin HPLC, Column: Thermoquest, hyperprep HS C18, 8 um, 250x21.2 mm. Eluents: 5% B/A to 100% B/A in 25 min.

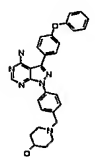
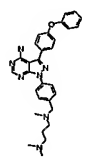
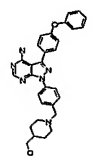
(B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 21 mL/min.) to give *cis*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)(1*H*-benzo[*d*]imidazol-2-yl)methanol (2 mg, 0.4%). ^{1}H NMR ($CDCl_3$) δ 1.68 (m, 2H), 1.81 (m, 2H), 2.01 (m, 2H), 2.13 (m, 2H), 2.33 (s, 3H), 2.42 (m, 2H), 2.64 (m, 7H), 4.68 (bs, 3H), 4.93 (m, 1H), 5.77 (bs, 2H), 6.06 (s, 1H), 7.20 (m, 2H), 7.52 (m, 2H), 7.58 (m, 4H), 8.32 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.): MH^+=538.3, R_t=3.80 min.

Examples 735-746

Examples 735-746 were prepared from 4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]benzaldehyde using the following method:

4-[4-Amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]benzaldehyde (50 mg, 0.123 mmol), the appropriate amine (0.246 mmol), sodium triacetoxyborohydride (78mg, 0.368 mmol) and glacial acetic acid (32 mg, 0.540 mmol) were mixed in THF (3 mL). After shaking at room temperature overnight on a J-Kem shaker, further amount of the amine (0.246 mmol), sodium triacetoxyborohydride (78mg, 0.368 mmol) and glacial acetic acid (32 mg, 0.540 mmol) were added again and the reaction mixtures were shaken at room temperature overnight. The solvent was evaporated and dichloromethane was added followed by sodium hydroxide (1.0N). The layers were separated with the aid of Empore Cartridge. The organic layer was evaporated and the residue was purified by reverse phase preparative LC/MS (Micromass- Column: Hypersil BDS, C18, 5 um, 100x21.2 mm. Eluents: 15% B/A to 100% B/A in 7 min.(B: acetonitrile, A: 50 mM ammonia acetate buffer, PH 4.5) , 25 mL/min.). After removing solvent, the resulting solid was dissolved in dichloromethane/sodium hydroxide (1.0N) mixture and the layers were separated. The organic layer was evaporated to give the corresponding product, detailed on the following table.

Entry	Structure	Compound name	MH^+	R_t (mins)	Qty (mg)
735		2-({4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]benzyl}amino)-1-ethanol	453.2	2.05	10
736		2-({4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]benzyl}amino)-2-methyl-1-propanol	481.2	2.12	12
737		4-({4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]benzyl}amino)-1-butanol	481.2	2.05	10
738		*N*1-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]benzyl}-*N*2,*N*2-dimethyl-1,2-ethanediamine	480.2	2.03	2
739		1-(4-{[(3-methoxypropyl)amino]methyl}phenyl)-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine	481.2	2.3	2
740		1-(4-{[(2-methoxyethyl)amino]methyl}phenyl)-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine	467.2	2.22	10
741		3-(4-phenoxyphenyl)-1-[4-(1,3-thiazolan-3-ylmethyl)phenyl]-1H-pyrazolo[3,4-*d*]pyrimidin-4-amine	481.2	4.2	3
742		2-[{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]benzyl}(2-hydroxyethyl)amino]-1-ethanol	497.2	2.02	2
743		*N*1-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]benzyl}-*N*1,*N*2,*N*2-trimethyl-1,2-ethanediamine	494.3	2.47	8

744		1-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]benzyl}-4-piperidinol	493.3	2.13	2
745		*N*1-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]benzyl}-*N*1,*N*3,*N*3-trimethyl-1,3-propanediamine	508.3	1.78	9
746		(1-{4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]benzyl}-4-piperidyl)methanol	507.3	2.12	9

Example 747: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide, dimaleate salt

*N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide (380 mg, 0.717 mmol) was dissolved in hot ethyl acetate (70 mL) and maleic acid (167 mg, 1.435 mmol) in hot ethyl acetate (3 mL) was added. The reaction mixture was stirred at room temperature for 3 hours. The solid was collected by filtration to give *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl) benzamide, dimaleate salt (489 mg, 90%). ^{1}H NMR (DMSO-d_6) δ 2.15 (m, 2H), 2.41 (m, 2H), 3.23 (m, 2H), 3.94 (s, 3H), 5.09(m, 1H), 6.14 (m, s, 4H), 7.33 (m, 2H), 7.76 (m, 1H), 7.88 (m, 1H), 7.99 (m, 1H), 8.28 (s, 1H), 8.33 (m, 2H), 8.70 (bs, 1H), 9.92 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.): MH^+=530.2, R_t=2.03 min.

Intermediate 6: *N*1-4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-2-fluoro-4-(trifluoromethyl)benzamide

A. *tert*-Butyl 4-[4-amino-3-(4-[2-fluoro-4-(trifluoromethyl)benzoyl]amino-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate

2-Fluoro-4-(trifluoromethyl)-1-benzenecarbonyl chloride (3.05 mL, 20.2 mmol) in dichloromethane (25 mL) was added to a solution of *tert*-butyl 4-[4-amino-3-(4-amino-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate (8.77 g, 20.0 mmol) in pyridine (50 mL) at 0°C. After 5 minutes, the ice water bath was removed and the reaction mixture stirred at room temperature for 1 hours. 2-Fluoro-4-(trifluoromethyl)-1-benzenecarbonyl chloride (0.5 mL, 3.31 mmol) was added and the reaction mixture was stirred for addition 30 minutes. The solvent was evaporated and the residue was dissolved in dichloromethane. The organic layer was washed with water, brine then dried over $MgSO_4$. The solvent was evaporated and the residue was purified by flash column chromatography using ethyl acetate/dichloromethane (80:20 to 100:0) as mobile phase to give *tert*-Butyl 4-[4-amino-3-(4-[2-fluoro-4-(trifluoromethyl)benzoyl]amino-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate (11.2 g, 89%). ^{1}H NMR ($CDCl_3$-*d*) δ 1.48 (s, 9H), 2.04 (m, 2H), 2.30 (m, 2H), 2.98 (m, 2H), 4.05 (s, 3H), 4.32 (m, 2H), 4.95 (m, 1H), 5.89 (bs, 2H), 7.33 (m, 2H), 7.51 (d, J=11.62 Hz, 1H), 7.61 (d, J=8.21Hz, 1H), 8.36 (m, 2H), 8.72 (d, J=8.18 Hz, 1H), 9.32 (d, J=14.39 Hz, 1H).

B. *N*1-4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-2-fluoro-4-(trifluoromethyl)benzamide

A mixture of trifluoroacetic acid/dichloromethane (20:80, 100 mL) was added to a solution of *tert*-Butyl 4-[4-amino-3-(4-[2-fluoro-4-(trifluoromethyl)benzoyl]amino-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate (11.2, 17.79 mmol) in dichloromethane (50 mL) at 0°C. 15 minutes later, the ice-bath was removed and the reaction mixture was stirred at room temperature for 3 hours. The solvents were evaporated and the residue was dissolved in dichloromethane. Saturated sodium bicarbonate solution was added to adjust the pH to about 8. The suspension was lyophilized. Water (100 ml) was added and the aqueous was extracted with dichloromethane repetitively to give *N*1-4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-2-

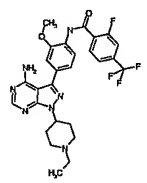
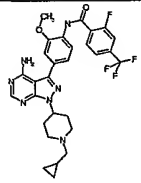
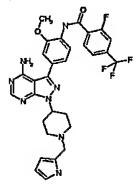
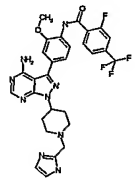
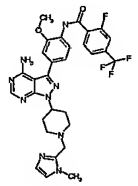
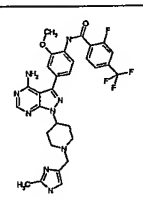
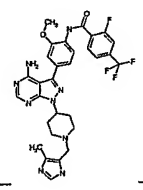
fluoro-4-(trifluoromethyl)benzamide (9.12 g, 97%). ^{1}H NMR (DMSO-d_6) δ 1.85 (m, 2H), 2.12 (m, 2H), 2.70 (m, 2H), 3.14 (m, 2H), 3.94 (s, 3H), 4.77 (m, 1H), 7.32 (m, 2H), 7.75 (d, J=8.02 Hz, 1H), 7.89 (d, J=10.31Hz, 1H), 8.00 (m, 1H), 8.24 (s, 1H), 8.31 (d, J=8.16 Hz, 1H), 9.90 (s, 1H).

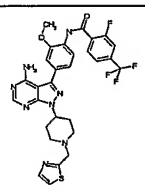
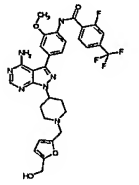
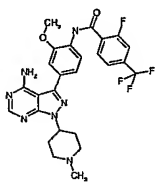
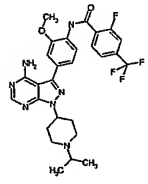
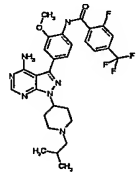
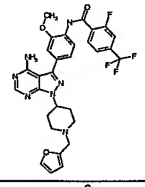
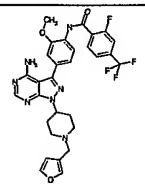
Examples 748-786

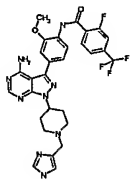
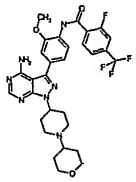
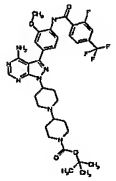
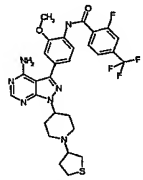
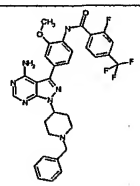
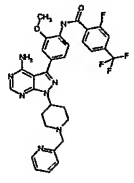
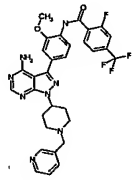
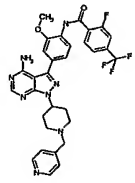
Examples 748-828 were derived from *N*1-4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-2-fluoro-4-(trifluoromethyl)benzamide (Intermediate 6) using method A or method B:Method A: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide (100 mg, 0.189 mmol), the appropriate aldehyde (0.378 mmol), sodium triacetoxyborohydride (120mg, 0.567 mmol) and glacial acetic acid (48 mg, 0.378 mmol) were mixed in 1,2-dichloroethane (4 mL). After shacking at room temperature overnight, further amount of the aldehyde (0.378 mmol), sodium triacetoxyborohydride (120mg, 0.567) and glacial acetic acid (48 mg, 0.378 mmol) were added again and the reaction mixtures were shaken at room temperature overnight. The solvent was evaporated and the residue was purified either by flash column chromatography using dichloromethane/methanol (95:5 to 70:30) or by reverse phase preparative HPLC (Rainin HPLC, Column: Thermoquest, hyperprep HS C18, 8 um, 250x21.2 mm. Eluents: 5% B/A to 100% B/A in 25 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 21 mL/min.) to give the corresponding product, detailed on the following table.

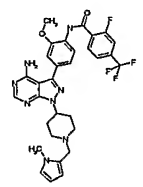
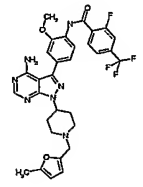
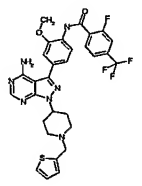
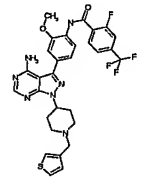
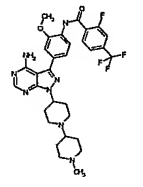
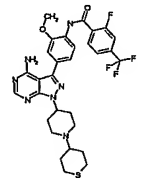
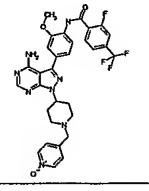
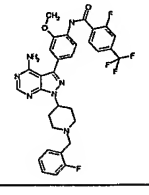
Method B: *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide (100 mg, 0.189 mmol), the appropriate ketone or some less reactive aldehyde (0.378 mmol), sodium triacetoxyborohydride (120mg, 0.567 mmol) and glacial acetic acid (48 mg, 0.378 mmol) were mixed in 1,2-dichloroethane (4 mL). The reaction mixture was shaken at 70°C for 4 hours. The solvent was evaporated and the residue was purified ether by flash column chromatography using dichloromethane/methanol (95:5 to 70:30) or by reverse phase preparative HPLC (Rainin HPLC, Column: Thermoquest, hyperprep HS C18, 8 um, 250x21.2 mm. Eluents: 5% B/A to 100% B/A in 25 min.

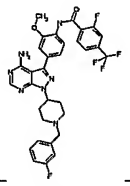
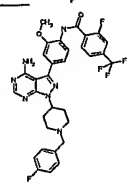
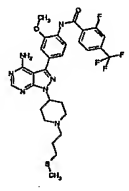
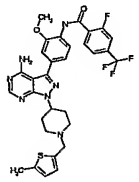
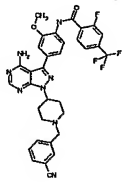
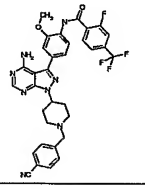
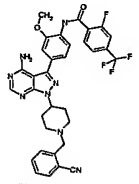
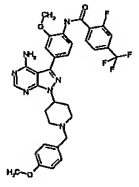
(B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 21 mL/min.) to give the corresponding product, detailed on the following table.

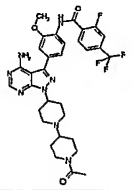
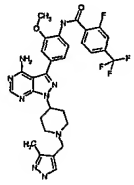
	Structure	Compound name	MH^+	R_t (mins)	Qty (mg)	Method
748		*N*1-{4-[4-amino-1-(1-ethyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide	MH⁻ 556.1	2.07	56	A
749		*N*1-(4-{4-amino-1-[1-(cyclopropylmethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide	MH⁻ 582.1	2.22	80	A
750		*N*1-(4-{4-amino-1-[1-(1*H*-2-pyrrolylmethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide, acetate salt	MH⁻ 607.0	2.45	60	A
751		*N*1-(4-{4-amino-1-[1-(1*H*-2-imidazolylmethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide	MH+ 610.2	2.17	68	B
752		N1-[4-(4-amino-1-{1-[(1-methyl-1H-2-imidazolyl)methyl]-4-piperidyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-(trifluoromethyl)benzamide, acetate salt	MH⁻ 622.0	2.23	56	A
753		N1-[4-(4-amino-1-{1-[(2-methyl-1H-4-imidazolyl)methyl]-4-piperidyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-(trifluoromethyl)benzamide, acetate salt	MH⁻ 622.0	2.05	32	A
754		*N*1-[4-(4-amino-1-{1-[(4-methyl-1*H*-5-imidazolyl)methyl]-4-piperidyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-	MH⁻ 622.0	2.08	84	A

		(trifluoromethyl)benzamide, acetate salt				
755		*N*1-(4-{4-amino-1-[1-(1,3-thiazol-2-ylmethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide	MH^- 625.1	3.15	73	A
756		*N*1-{4-[4-amino-1-(1-{[5-(hydroxymethyl)-2-furyl]methyl}-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide	MH^- 638.1	2.20	36	A
757		*N*1-{4-[4-amino-1-(1-methyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide	MH^- 542.2	2.03	67	A
758		*N*1-{4-[4-amino-1-(1-isopropyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide	MH^- 570.1	2.08	58	B
759		*N*1-{4-[4-amino-1-(1-isobutyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide, acetate salt	MH^- 584.0	2.43	54	A
760		*N*1-(4-{4-amino-1-[1-(2-furylmethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide	MH^- 608.1	2.63	82	A
262		*N*1-(4-{4-amino-1-[1-(3-furylmethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide	MH^+ 610.2	2.43	54	A

761		*N*1-(4-{4-amino-1-[1-(1*H*-4-imidazolylmethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide, acetate salt	MH^- 608.0	1.90	55	A
762		*N*1-{4-[4-amino-1-(1-tetrahydro-2*H*-4-pyranyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide	MH^+ 614.2	2.13	91	B
763		*tert*-butyl 4-{4-[4-amino-3-(4-{[2-fluoro-4-(trifluoromethyl)benzoyl]amino}-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidyl}-1-piperidinecarboxylate	MH^+ 713.3	2.57	74	B
764		*N*1-{4-[4-amino-1-(1-tetrahydro-3-thiophenyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide	MH^+ 616.2	2.53	102	B
765		*N*1-{4-[4-amino-1-(1-benzyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide	MH^- 618.0	2.67	69	A
766		*N*1-(4-{4-amino-1-[1-(2-pyridylmethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide, acetate salt	MH^- 619.1	2.32	84	A
767		*N*1-(4-{4-amino-1-[1-(3-pyridylmethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide	MH^- 619.1	2.32	77	A
768		*N*1-(4-{4-amino-1-[1-(4-pyridylmethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide	MH^- 619.1	2.63	81	A

769		*N*1-[4-(4-amino-1-{1-[(1-methyl-1H-2-pyrrolyl)methyl]-4-piperidyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-(trifluoromethyl)benzamide, acetate salt	MH^- 621.2	2.52	35	B
770		*N*1-[4-(4-amino-1-{1-[(5-methyl-2-furyl)methyl]-4-piperidyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-(trifluoromethyl)benzamide, acetate salt	MH^- 622.1	2.65	78	A
771		*N*1-(4-{4-amino-1-[1-(2-thienylmethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide	MH^- 624.0	3.00	57	B
772		*N*1-(4-{4-amino-1-[1-(3-thienylmethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide, acetate salt	MH^+ 626.2	2.55	87	A
773		*N*1-[4-(4-amino-1-{1-[(1-methypiperidin-4-yl]-4-piperidyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-(trifluoromethyl)benzamide, diacetate salt	MH^+ 627.2	1.80	72	B
774		*N*1-{4-[4-amino-1-(1-tetrahydro-2H-4-thiopyranyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide	MH^+ 630.2	2.37	20	B
775		4-({4-[4-amino-3-(4-{[2-fluoro-4-(trifluoromethyl)benzoyl]amino}-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidino}methyl)-1-pyridine-N-oxide	MH^+ 637.2	2.13	93	A
776		*N*1-(4-{4-amino-1-[1-(2-fluorobenzyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide	MH^+ 638.2	3.13	84	A

777		*N*1-(4-{4-amino-1-[1-(3-fluorobenzyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide	MH^+ 638.2	3.25	77	A
778		*N*1-(4-{4-amino-1-[1-(4-fluorobenzyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide	MH^+ 638.2	2.87	88	A
779		*N*1-[4-(4-amino-1-{1-[3-(methylsulfanyl)propyl]-4-piperidyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-(trifluoromethyl)benzamide	MH^+ 618.2	2.42	76	A
780		*N*1-[4-(4-amino-1-{1-[(5-methyl-2-thienyl)methyl]-4-piperidyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-(trifluoromethyl)benzamide	MH^+ 640.2	3.23	73	A
781		*N*1-(4-{4-amino-1-[1-(3-cyanobenzyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide	MH^+ 645.2	3.28	57	A
782		*N*1-(4-{4-amino-1-[1-(4-cyanobenzyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide	MH^+ 645.2	3.32	62	A
783		*N*1-(4-{4-amino-1-[1-(2-cyanobenzyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide	MH^+ 645.2	3.78	62	A
784		*N*1-(4-{4-amino-1-[1-(4-methoxybenzyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide	MH^+ 650.2	2.63	45	A

785		*N*1-[4-(4-amino-1-{1-[(1-acetyl-piperidin-4-yl]-4-piperidyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-(trifluoromethyl)benzamide	MH^+ 655.2	2.02	71	B
786		*N*1-[4-(4-amino-1-{1-[(3-methyl-1H-4-pyrazolyl)methyl]-4-piperidyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-(trifluoromethyl)benzamide, acetate salt	MH^+ 624.2	2.07	109	A

Example 787: Methyl 2-4-[4-amino-3-(4-[2-fluoro-4-(trifluoromethyl)benzoyl]amino-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidinoacetate

*N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide (122g, 0.230 mmol), methyl 2-bromoacetate (33 uL, 0.346 mmol) and cesium carbonate (150 mg, 0.461 mmol) was mixted with DMF (2 mL). The mixture was heated to 85°C for 2 hours. LC/MS showed formation of two new peaks, one of them was bis-alkylated one and the other the desired product. The crude mixture was purified by reverse phase preparative HPLC (Rainin HPLC, Column: Thermoquest, hyperprep HS C18, 8 um, 250x21.2 mm. Eluents: 5% B/A to 100% B/A in 25 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 21 mL/min.) to give methyl 2-4-[4-amino-3-(4-[2-fluoro-4-(trifluoromethyl)benzoyl]amino-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidinoacetate (60 mg, 43%). ^{1}H NMR (DMSO-d_6) δ 1.91 (m, 2H), 2.27 (m, 2H), 2.42 (m, 2H), 2.98 (m, 2H), 3.32 (s, 2H), 3.64 (s, 3H), 3.95 (s, 3H), 4.67 (m, 1H), 7.32 (m, 2H), 7.75 (d, J=7.96Hz, 1H), 7.89 (d, J=10.35 Hz, 1H), 8.00 (s, 1H), 8.24 (s, 1H), 8.30 (d, J=8.13 Hz, 1H), 9.89 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.): MH^+=602.2, R_t=2.80 min.

Example 788: *trans*-3-[4-(1H-benzo[d]imidazol-1-ylmethyl)-3-methoxyphenyl]-1-[4-(4-methylpiperazino)cyclohexyl]-1H-pyrazolo[3,4-d]pyrimidin-4-amine

A. 1-(4-Bromobenzyl)-1*H*-benzo[*d*]imidazole

1-Bromo-4-(bromomethyl)benzene (2.50 g, 10 mmol), 1*H*-benzo[*d*]imidazole (1.181g, 10.0 mmol), potassium hydroxide (0.561 g, 10.0 mmol), potassium carbonate (1.382 g, 10.0 mmol) and tetrabutylammonium bromide (0.161 g, 0.5 mmol) was mixed in xylenes (60 mL). The reaction mixture was heated at 139°C overnight. The hot reaction mixture was filtered and washed with hot xylenes. The solvent was evaporated and the residue was purified by flash column chromatography using dichloromethane/methanol (95:5 to 80:20) as mobile phase to give 1-(4-Bromobenzyl)-1*H*-benzo[*d*]imidazole (1.193 g, 42%). ^{1}H NMR ($CDCl_3$) δ 5.31 (s, 2H), 7.05 (m, 2H), 7.28 (m, 3H), 7.46 (m, 2H), 7.82 (m, 1H), 7.95 (s, 1H).

B. 1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl]-1*H*-benzo[*d*]imidazole

A mixture of 1-(4-Bromobenzyl)-1*H*-benzo[*d*]imidazole (1.193 mg, 4.15 mmol), diboron pinacol ester (1.27 g, 4.98 mmol), [1.1' bis(diphenylphosphino)ferrocene] dichloropalladium (II) complex with dichloromethane (1:1) (0.10g, 0.12 mol) and potassium acetate (1.22 g, 12.46 mol) in *N,N*-dimethylformamide (25 mL) was heated at 85° C under an atmosphere of nitrogen for 16 hours. The mixture was allowed to cool to ambient temperature and the solvent removed under reduced pressure. Dichloromethane (20 mL) was added to the residue and the resulting solid was removed by filtration through a pad of celite. The filtrate was concentrated and the residue was purified by flash chromatography on silica using dichloromethane/ methanol (98:2 to 95:5) as mobile phase to give 1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl]-1*H*-benzo[*d*]imidazole (1.38 g, 100%): ^{1}H NMR ($CDCl_3$) δ 1.27 (s, 12H), 5.33 (s, 2H), 7.06 (d, J=8.24Hz, 2H), 7.28 (d, J=8.34 Hz, 2H), 7.84 (d, J=7.70Hz, 1H), 8.01 (s, 1H).

C. *trans*-3-[4-(1*H*-benzo[*d*]imidazol-1-ylmethyl)-3-methoxyphenyl]-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-

amine

trans-3-Iodo-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (200 mg, 0.453 mmol), 1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl]-1*H*-benzo[*d*]imidazole (303 mg, 0.906 mmol), palladium tetrakistriphenyphosphine (0.31 mg, 0.027 mmol) and sodium carbonate (155 mg, 1.09 mmol) were mixed with ethylene glycol dimethyl ether (5 mL) and water (2.5 mL). The reaction mixture was heated at reflux overnight under nitrogen. The solvent was removed and the residue was purified by reverse phase preparative HPLC (Rainin HPLC, Column: Thermoquest, hyperprep HS C18, 8 um, 250x21.2 mm. Eluents: 5% B/A to 100% B/A in 25 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 21 mL/min.) to give *trans*-3-[4-(1*H*-benzo[*d*]imidazol-1-ylmethyl)-3-methoxyphenyl]-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (35 mg, 15%). ^{1}H NMR (DMSO-d_6) δ 1.46 (m, 2H), 1.95 (m, 10H), 2.13 (s, (3H), 2.32 (m, 5H), 4.62 (m, 1H), 5.78 (s, 2H), 7.22 (m, 2H), 7.49 (m, 2H), 7.62 (m, 4H), 8.22 (s, 1H), 8.44 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC-Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.): MH^+=522.3, R_t=0.82 min.

Example 789: *N*1-(4-{4-amino-1-[1-(2-methoxyethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide, acetate salt

*N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide (100g, 0.189 mmol), 2-bromoethyl methyl ether (20 uL, 0.208 mmol) and potassium carbonate (52 mg, 0.378 mmol) was mixed in DMF (2 mL). The mixture was heated at 65°C overnight. The crude mixture was purified by reverse phase preparative HPLC (Rainin HPLC, Column: Thermoquest, hyperprep HS C18, 8 um, 250x21.2 mm. Eluents: 5% B/A to 100% B/A in 25 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 21 mL/min.) to give *N*1-(4-{4-amino-1-[1-(2-methoxyethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide, acetate salt (75 mg, 68%). ^{1}H NMR (DMSO-d_6) δ 1.90

(m, 2H), 2.22 (m, 4H), 2.54 (m, 2H), 3.02 (m, 2H), 3.26 (s, 3H), 3.46 (m, 2H), 3.94 (m, s, 3H), 4.66 (m, 1H), 7.30 (d, J=8.19Hz, 1H), 7.34 (s, 1H), 7.74 (d, J=7.84Hz, 1H), 7.90 (d, J=10.33Hz, 1H), 7.99 (m, 1H), 8.24 (s, 1H), 8.30 (d, J=8.23 Hz, 1H), 9.89 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.): MH^+=587.2, R_t=2.17 min.

Example 790: *N*1-(4-{4-amino-1-[1-(cyanomethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide

*N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide (100g, 0.189 mmol), 2-bromoacetonitrile (14 uL, 0.208 mmol) and cesium carbonate (52 mg, 0.378 mmol) was mixed in DMF (2 mL). The mixture was stirred at room temperature overnight. The crude mixture was purified by reverse phase preparative HPLC (Rainin HPLC, Column: Thermoquest, hyperprep HS C18, 8 um, 250x21.2 mm. Eluents: 5% B/A to 100% B/A in 25 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 21 mL/min.) to give, *N*1-(4-{4-amino-1-[1-(cyanomethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl) benzamide (68 mg, 64%). ^{1}H NMR (DMSO-d_6) δ 1.99 (m, 2H), 2.27 (m, 2H), 2.45 (m, 2H), 2.99 (m, 2H), 3.80 (s, 2H), 3.94 (s, 3H), 4.68 (m, 1H), 7.30 (d, J=8.21Hz, 1H), 7.34 (s, 1H), 7.75 (d, J=8.26Hz, 1H), 7.90 (d, J=10.51Hz, 1H), 7.99 (m, 1H), 8.25 (s, 1H), 8.30 (d, J=8.18 Hz, 1H), 9.90 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.): MH^+=569.2, R_t=3.03 min.

Example 791: *N*1-(4-{4-amino-1-[1-(2-amino-2-oxoethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide, acetate salt

*N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-(trifluoromethyl)benzamide (100g, 0.189 mmol), 2-

bromoacetamide (28 mg, 0.208 mmol) and cesium carbonate (123 mg, 0.378 mmol) was mixed in DMF (2 mL). The mixture was stirred at room temperature overnight. The crude mixture was purified by reverse phase preparative HPLC (Rainin HPLC, Column: Thermoquest, hyperprep HS C18, 8 um, 250x21.2 mm. Eluents: 5% B/A to 100% B/A in 25 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 21 mL/min.) to give *N*1-(4-{4-amino-1-[1-(2-amino-2-oxoethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-2-fluoro-4-(trifluoromethyl)benzamide, acetate salt (70 mg, 63%). ^{1}H NMR (DMSO-d_6) δ 1.90 (m, 5H), 2.34 (m, 4H), 2.93 (s, 2H), 2.99 (m,2H), 3.94 (s, 3H), 4.69 (m, 1H), 7.12 (s, 1H), 7.25 (s, 1H), 7.30 (d, J=8.15Hz, 1H), 7.34 (s, 1H), 7.75 (d, J=8.15Hz, 1H), 7.87 (d, J=10.30Hz, 1H), 7.99 (m, 1H), 8.25 (s, 1H), 8.31 (d, J=8.14 Hz, 1H), 9.90 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, pH 4.5), 0.8 mL/min.): MH^+=587.2, R_t=2.17 min.

Example 792: 1-(1-methyl-3-piperidyl)-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

A solution of racemic 3-iodo-1-(1-methyl-3-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.050 g, 0.00014 mol) in dimethoxyethane (2.5 mL) and water (5 mL) was treated with 4-phenoxyphenylboronic acid (0.033 g, 0.00015 mol), sodium carbonate (0.037 g, 0.00037 mol) and tetrakis (triphenylphosphine) palladium (0) (0.016 g, 0.000014 mol) at 80° C for 18 hours. The organic solvent was removed *in vacuo*, and the crude material was purified by preparative RP-HPLC (Rainin C18, 8μm, 300 A, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M ammonium acetate over 15 min, 21 ml/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyopholyzed to give 1-(1-methyl-3-piperidyl)-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate as a white solid (0.040 g, 0.00009 mol).

^{1}H NMR (DMSO-d_6, 400MHz) δ 8.24 (s, 1H), 7.65 (d, 2H), 7.43 (t, 2H), 7.10- 7.22 (m, 5H), 4.74-4.84 (m, 1H), 2.94 (dd, 1H), 2.79 (d, 1H), 2.36 (t, 1H), 2.22 (s, 3H), 1.89 (s, 3H), 1.86-2.01 (m, 3H), 1.76-1.84 (m, 1H), 1.60-1.75 (m, 1H);

RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 13.74 min.;
MS: MH^+ 401.

Example 793: 1-[1-(2-methoxyethyl)-3-piperidyl]-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

A solution of racemic 3-iodo-1-[1-(2-methoxyethyl)-3-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.050 g, 0.00012 mol) in dimethoxyethane (2.5 mL) and water (5 mL) was treated with 4-phenoxyphenylboronic acid (0.029 g, 0.00014 mol), sodium carbonate (0.033 g, 0.00031 mol) and tetrakis(triphenylphosphine) palladium (0) (0.014 g, 0.00001 mol) at 80° C for 20 hours. The organic solvent was removed *in vacuo*, and the crude material was purified by preparative RP-HPLC (Rainin C18, 8μm, 300 A, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M ammonium acetate over 15 min, 21 ml/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyopholyzed to give 1-[1-(2-methoxyethyl)-3-piperidyl]-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate as a white solid (0.038 g, 0.00007 mol).
^{1}H NMR (DMSO-d_6, 400MHz) δ 8.24 (s, 1H), 7.65 (d, 2H), 7.43 (t, 2H), 7.09- 7.22 (m, 5H), 4.71-4.82 (m, 1H), 3.44 (t, 2H), 3.21 (s, 3H), 3.04 (dd, 1H), 2.91 (d, 1H), 2.47-2.60 (m, 3H), 1.94-2.09 (m, 3H), 1.89 (s, 3H), 1.75-1.84 (m, 1H), 1.57-1.74 (m, 1H);
RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 14.26 min.;
MS: MH^+ 445.

Example 794: *Trans* 1-{4-[4-amino-3-(3-chloro-4-{[4-(trifluoromethyl)benzoyl]amino}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl}-4-methylhexahydropyrazinediium dimaleate

A. *Tert*-butyl N-(4-bromo-2-chlorophenyl)carbamate

A solution of 4-bromo-2-chloroaniline (5.00 g, 0.0242 mol) in tetrahydrofuran (50 mL) was reacted with a 1.0 M solution of sodium bis(trimethylsilyl)amide in tetrahydrofuran (53.2 mL, 0.0532 mol). The mixture was stirred 15 minutes at ambient

temperature. Di-*tert*-butyl dicarbonate (6.34 g, 0.0290 mol) was added and the solution was stirred for 2 hours. The solvent was removed *in vacuo*, and the crude material was purified by flash column chromatography on silica using heptane /ethyl acetate (4:1). The solvent was removed *in vacuo* to give *tert*-butyl *N*-(4-bromo-2-chlorophenyl)carbamate as a white solid (4.214 g, 0.0137 mol).

^{1}H NMR (DMSO-d_6, 400MHz) δ 8.75 (s, 1H), 7.71 (d, 1H), 7.54 (d, 1H), 7.50 (dd, 1H), 1.46 (s, 9H);

TLC (heptane/ethylacetate 4:1) R_f 0.54.

B. *Tert*-butyl *N*-[2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate

A mixture of *tert*-butyl *N*-(4-bromo-2-chlorophenyl)carbamate (2.10 g, 0.00685 mol), diboron pinacol ester (2.09 g, 0.00822 mol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (0.17 g, 0.00021 mol) and potassium acetate (2.02 g, 0.02055 mol) in *N,N*-dimethylformamide (50 ml) was heated at 80°C under a nitrogen atmosphere for 6 hours. The solvent was removed *in vacuo*. The residue was triturated with heptane (70 mL) and the resulting solids were removed by filtration through a pad of Celite ® 521. The heptane was removed *in vacuo* to give *tert*-butyl *N*-[2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate as a grey solid (1.93 g, 0.00546 mol):

^{1}H NMR (DMSO-d_6, 400MHz) δ 8.65 (s, 1H), 7.74 (d, 1H), 7.61 (d, 1H), 7.56 (dd, 1H), 1.47 (s,9H), 1.29 (s, 12H).

C. *Trans tert*-butyl *N*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-chlorophenyl)carbamate

A mixture of *trans* 3-iodo-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (2.20 g, 0.00498 mol), *tert*-butyl *N*-[2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (1.93 g, 0.00548 mol), sodium carbonate (1.32 g, 0.01245 mol) in 1,2-dimethoxyethane (50 mL) and water (100 mL) was stirred rapidly and tetrakis(triphenylphosphine)palladium(0) (0.345 g, 0.00030 mol) was added. The reaction mixture was stirred 6 hours at 80°C, after which time additional tetrakis(triphenylphosphine)palladium(0) (0.345 g, 0.00030 mol) was

added. The reaction mixture was stirred an additional 16 hours at 80°C. The solvents were removed *in vacuo* and the residue was partitioned between ethyl acetate (100 mL) and saturated aqueous sodium bicarbonate (200 mL). The phases were separated and the aqueous phase was extracted with ethyl acetate (3 x 75 mL). The combined organic phases were dried over magnesium sulfate, and the solvent was removed *in vacuo*. The product was purified by flash column chromatography on silica using dichloromethane/methanol/ammonium hydroxide (90:10:0.5). The solvent was removed *in vacuo* to give trans *tert*-butyl *N*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-chlorophenyl)carbamate as a white solid (1.993 g, 0.00368 mol):

^{1}H NMR (DMSO-d_6, 400MHz) δ 8.76 (s, 1H), 8.23 (s, 1H), 7.80 (d, 1H), 7.68 (d, 1H), 7.57 (dd, 1H), 4.58-4.71 (m, 1H), 2.15 (s, 3H), 1.89-2.61 (m, 15H), 1.49 (s, 9H), 1.40-1.48 (m, 2H); TLC (dichloromethane/methanol = 90:10) R_f 0.13, MS: M^+ 541.

D. *Trans* 3-(4-amino-3-chlorophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

Trans tert-butyl *N*-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-chlorophenyl)carbamate (1.993 g, 0.00368 mol) was added to a solution of 20% trifluoracetic acid in dichloromethane. The mixture was stirred for 2 hours at ambient temperature. The solvent was removed *in vacuo* and the residue was dissolved in dichloromethane (50 mL) and washed with a 1.0 M aqueous solution of sodium hydroxide (2 x 25 mL). The organic layer was dried over magnesium sulfate and the solvent was removed *in vacuo* to give *trans* 3-(4-amino-3-chlorophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (1.564 g, 0.00355 mol) as a white solid.

^{1}H NMR (DMSO-d_6, 400MHz) δ 8.20 (s, 1H), 7.45 (d, 1H), 7.31 (dd, 1H), 6.92 (d, 1H), 4.57-4.63 (m, 1H), 2.23-2.55 (m, 9H), 2.14 (s, 3H), 1.89-2.08 (m, 6H), 1.38-1.52 (m, 2H);

TLC (dichloromethane/methanol = 90:10) R_f 0.08;

MS: MH^+ 441.

E. *Trans N*1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-

pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-chlorophenyl)-4-(trifluoromethyl)benzamide dimaleate

To a mixture of 3-(4-amino-3-chlorophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.200 g, 0.00045 mol) in pyridine (5 mL) at -10° C 4-(trifluoromethyl)-1-benzenecarbonyl chloride (0.188 g, 0.00090 mol) was added dropwise, keeping the temperature below -5° C. The mixture was stirred at -10° C for 15 minutes, and then at ambient temperature for 18 hours. After addition of an 1N aqueous solution of sodium hydroxide (1.0 mL) the mixture was stirred one hour. The solvent was removed *in vacuo*, and the residue was partitioned between ethyl acetate (15 mL) and water (30 mL). The layers were separated and the aqueous phase was extracted with ethyl acetate (15 mL), and the combined organic layers were dried over magnesium sulfate. The solvent was removed *in vacuo*, and the residue was purified by preparative RP-HPLC (Rainin C18, 8μm, 300 A, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M ammonium acetate over 15 min, 21 ml/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyopholyzed to give the purified free base (0.032 g, 0.000052 mol). The free base was dissolved in absolute ethanol (4 mL) and heated to reflux. After addition of a solution of maleic acid (0.018 g, 0.000156mol) in absolute ethanol (1 mL) the solution was refluxed for further 15 minutes. The mixture was cooled to ambient temperature, and the resulting precipitate was filtered, washing with a minimal amount of absolute ethanol. The precipitate was dried *in vacuo* to give *trans N*1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-chlorophenyl)-4-(trifluoromethyl)benzamide dimaleate as a white solid (0.020 g, 0.00002 mol):

^{1}H NMR (DMSO-d_6, 400MHz) δ 10.42 (s, 1H), 8.26 (s, 1H), 8.20 (d, 2H), 7.96 (d, 2H), 7.80-7.83 (m, 2H), 7.46 (dd, 1H), 6.80-7.20 (b, 2H), 6.13 (s, 4H), 4.61-4.73 (m, 1H), 2.52-2.64 (m, 4H), 2,23-2.46 (m, 5H), 2.16 (s, 3H), 1.90-2.10 (m, 6H), 1.42-1.56 (m, 2H);

RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 14.97 min.;

MS: MH^+ 613.

Example 795: *Trans N*1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-chlorophenyl)-4-(trifluoromethoxy)benzamide dimaleate

To a mixture of 3-(4-amino-3-chlorophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.200 g, 0.00045 mol) in pyridine (5 mL) at -10° C 4-(trifluoromethoxy)-1-benzenecarbonyl chloride (0.203 g, 0.00091 mol) was added dropwise, keeping the temperature less than -5° C. The mixture was stirred at -10° C for 15 minutes and then at ambient temperature for 18 hours. After addition of an 1N aqueous solution of sodium hydroxide (1.0 mL) the mixture was stirred one hour. The solvent was removed *in vacuo*, and the residue was partitioned between ethyl acetate (15 mL) and water (30 mL). The layers were separated and the aqueous phase was extraxcted with ethyl acetate (15 mL), and the combined organic layers were dried over magnesium sulfate. The solvent was removed *in vacuo*, and the residue was purified by preparative RP-HPLC (Rainin C18, 8μm, 300 A, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M ammonium acetate over 15 min, 21 ml/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyopholyzed to give the purified free base (0.034 g, 0.000054 mol). The free base was dissolved in absolute ethanol (4 mL) and heated to reflux. A solution of maleic acid (0.019 g, 0.000162 mol) in absolute ethanol (1 mL) was added and the solution was refluxed for 15 minutes. The mixture was cooled to ambient temperature, and the resulting precipitate was filtered, washing with a minimal amount of absolute ethanol. The precipitate was dried *in vacuo* to give *trans N*1-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-chlorophenyl)-4-(trifluoromethoxy)benzamide dimaleate as a white solid (0.020 g, 0.00002 mol):

^{1}H NMR (DMSO-d_6, 400MHz) δ 10.29 (s, 1H), 8.26 (s, 1H), 8.14 (d, 2H), 7.78-7.87 (m, 2H), 7.68 (dd, 1H), 7.57 (d, 2H), 6.80-7.20 (b, 2H), 6.11 (s, 4H), 4.65-4.77 (m, 1H), 2.38-3.60 (m, 12H), 1.95-2.15 (m, 6H), 1.51-1.68 (m, 2H);

RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 15.41 min.;

MS: MH^+ 629.

Example 796: *Trans* 3-(3-chloro-4-{[(5-methyl-2-furyl)methyl]amino}phenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine
acetate

A mixture of 3-(4-amino-3-chlorophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.200 g, 0.00045 mol) in 1,2-dichloroethane (20 mL) was reacted with 5-methyl-2-furfural (0.052 g, 0.00048 mol), acetic acid (0.095 g, 0.00159 mol) and sodium triacetoxyborohydride (0.336 g, 0.00159 mol) at ambient temperature. An additional two equivalents of sodium triacetoxyborohydride (0.672 g, 0.00318 mol) were added in two 24 hour intervals. The solvents were removed *in vacuo* and the residue was partitioned between chloroform (25 mL) and saturated aqueous sodium bicarbonate (50 mL). The phases were separated and the aqueous phase was extracted with chloroform (2 x 25 mL). The combined organic phases were dried over magnesium sulfate, and the solvent was removed *in vacuo*. The residue was purified by preparative RP-HPLC (Rainin C18, 8μm, 300 A, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M ammonium acetate over 15 min, 21 ml/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyopholyzed to give *trans* 3-(3-chloro-4-{[(5-methyl-2-furyl)methyl]amino}phenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate as a white solid (0.129 g, 0.00022 mol):

^{1}H NMR (DMSO-d_6, 400MHz) δ 8.20 (s, 1H), 7.51 (d, 1H), 7.39 (dd, 1H), 6.93 (d, 1H), 6.20 (d, 1H), 6.14 (t, 1H), 5.98 (d, 1H), 4.55-4.66 (m, 1H), 4.38 (d, 2H), 2.23 (s, 3H), 2.18-2.61 (m, 10 H), 2.14 (s, 3H), 1.91 (s, 3H), 1.87-2.09 (m, 5H), 1.37-1.53 (m, 2H); RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 14.48 min.;

MS: MH^+ 535.

Example 797: *Trans* 3-{3-chloro-4-[(2-chloro-6-fluorobenzyl)amino]phenyl}-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-

amine acetate

A mixture of 3-(4-amino-3-chlorophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.200 g, 0.00045 mol) in 1,2-dichloroethane (20 mL) was reacted with 2-chloro-6-fluorobenzaldehyde (0.076 g, 0.00048 mol), acetic acid (0.095 g, 0.00159 mol) and sodium triacetoxyborohydride (0.336 g, 0.00159 mol) at ambient temperature. An additional three equivalents of sodium triacetoxyborohydride (1.008 g, 0.00477 mol) were added in three 24 hour intervals, after which time all the starting material had been consumed. The solvents were removed *in vacuo* and the residue was partitioned between chloroform (25 mL) and saturated aqueous sodium bicarbonate (50 mL). The phases were separated and the aqueous phase was extracted with chloroform (2 x 25 mL). The combined organic phases were dried over magnesium sulfate, and the solvent was removed *in vacuo*. The residue was purified by preparative RP-HPLC (Rainin C18, 8μm, 300 A, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M ammonium acetate over 15 min, 21 ml/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyopholyzed to give to give *trans* 3-{3-chloro-4-[(2-chloro-6-fluorobenzyl)amino]phenyl}-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate as a white solid (0.074 g, 0.00011 mol):

^{1}H NMR (DMSO-d_6, 400MHz) δ 8.20 (s, 1H), 7.52 (d, 1H), 7.35-7.47 (m, 4H), 6.99 (d, 1H), 5.75 (t, 1H), 4.55-4.66 (m, 1H), 4.57 (d, 2H), 2.25-2.61 (m, 11 H), 2.16 (s, 3H), 1.91 (s, 3H), 1.87-2.09 (m, 4H), 1.37-1.53 (m, 2H);

RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 15.97 min.;

MS: MH^+ 583.

Example 798: *Trans N*1-(4-{4-amino-1-[1-(1*H*-2-imidazolylcarbonyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(*trans*)-2-phenyl-1-cyclopropanecarboxamide maleate

A mixture of *N*1-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-phenyl-1-cyclopropanecarboxamide (0.200 g, 0.00041 mol) in toluene (10 mL) was reacted with 5*H*,10*H*-diimidazo[1,5-*a*:1,5-*d*]pyrazine-

5,10-dione (0.040 g, 0.00021 mol) at reflux for 18 hours. An additional equivalent of 5*H*,10*H*-diimidazo[1,5-*a*:1,5-*d*]pyrazine-5,10-dione was added and the mixture was refluxed an additional 6 hours. The solvent was removed *in vacuo* and the residue was purified by preparative RP-HPLC (Rainin C18, 8μm, 300 A, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M ammonium acetate over 15 min, 21 ml/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyopholyzed to give the free base (0.103 g, 0.00017 mol). The free base was dissolved in absolute ethanol (10 mL) and heated to reflux. After addition of a solution of maleic acid (0.030 g, 0.00034 mol) in absolute ethanol (1 mL) the solution was refluxed for 15 minutes, after which time a precipitate formed. The mixture was cooled to ambient temperature, and the resulting precipitate was filtered, washing with a minimal amount of absolute ethanol. The precipitate was dried *in vacuo* to give *trans N*1-(4-{4-amino-1-[1-(1*H*-2-imidazolylcarbonyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(*trans*)-2-phenyl-1-cyclopropanecarboxamide maleate as a white solid (0.055 g, 0.00008 mol):
^{1}H NMR (DMSO-d_6, 400MHz) δ 9.63 (s, 1H), 8.26 (s, 1H), 8.22 (d, 1H), 8.00 (b, 1H), 7.74 (b, 1H), 7.43-7.48 (m, 1H), 7.16-7.33(m, 7H), 6.21 (s, 2H), 4.97-5.13 (m, 1H), 2.91-3.47 (m, 4H), 2.53-2.65 (m, 1H), 2.30-2.45 (m, 1H), 2.07-2.26 (m, 2H), 1.95-2.07 (m, 2H), 1.45-1.50 (m, 1H), 1.28-1.32 (m, 1H);
RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 14.17 min.;
MS: MH^+ 578.

Example 799: *Cis N*1-(4-{4-amino-1-[4-(2-aminoethyl)-4-hydroxycyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(*trans*)2-phenyl-1-cyclopropanecarboxamide acetate

A. *Cis N*1-(4-{4-amino-1-[4-(cyanomethyl)-4-hydroxycyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(*trans*)-2-phenyl-1-cyclopropanecarboxamide

A mixture of *cis N*1-{4-[4-amino-1-(1-oxaspiro[2.5]oct-6-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-(*trans*)-2-phenylcyclopropane-1-carboxamide (0.605 g, 0.0012 mol), lithium perchlorate (0.189 g, 0.0018 mol) and potassium cyanide (0.116 g, 0.0018 mol) in acetonitrile (60 ml) was heated at 80°C

for two days. Cooled to ambient temperature, diluted with water (30 mL) and extracted with diethyl ether (3x 30 mL). The combined organic phases were dried over magnesium sulfate. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography on silica using dichloromethane/methanol (95:5). The solvent was removed *in vacuo* to give *cis N*1-(4-{4-amino-1-[4-(cyanomethyl)-4-hydroxycyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(*trans*)-2-phenyl-1-cyclopropanecarboxamide as a white solid (0.602 g, 0.0011 mol):

^{1}H NMR (DMSO-d_6, 400MHz) δ 9.64 (s, 1H), 8.23 (t, 2H), 7.31 (t, 2H), 7.25 (s, 1H), 7.17- (m, 4H), 4.61-4.62 (m, 1H), 3.91 (s, 1H), 2.66 (s, 2H), 2.55-2.62 (m, 1H), 2.31-2.45 (m, 3H), 1.58-1.89 (m, 6H), 1.45-1.53 (m, 1H), 1.28-1.38 (m, 1H);

RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 15.21 min.;

MS: MH^+ 538.

B. *Cis N*1-(4-{4-amino-1-[4-(2-aminoethyl)-4-hydroxycyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(*trans*)2-phenyl-1-cyclopropanecarboxamide acetate

To a solution of *cis N*1-(4-{4-amino-1-[4-(cyanomethyl)-4-hydroxycyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(*trans*)-2-phenyl-1-cyclopropane-carboxamide (0.200 g, 0.00037 mol) in methanol (20 ml) and ammonium hydroxide (1 mL) Raney nickel (0.5 mL) was added. The mixture was stirred 18 hours under a hydrogen atmosphere (1 atm). The reaction mixture was filtered through celite and the solvent was removed *in vacuo*. The residue was purified by preparative RP-HPLC (Rainin C18, 8µm, 300 A, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M ammonium acetate over 15 min, 21 ml/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyopholyzed to give *Cis N*1-(4-{4-amino-1-[4-(2-aminoethyl)-4-hydroxycyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(*trans*)2-phenyl-1-cyclopropanecarboxamide acetate as a white solid (0.045 g, 0.000083 mol).:

^{1}H NMR (DMSO-d_6, 400MHz) δ 9.64 (s, 1H), 8.23 (d, 1H), 8.22-8.24 (m, 1H), 7.17-7.33 (m, 7H), 4.65-4.67 (m, 1H), 3.91 (s, 3H), 2.84-2.91 (m, 1H), 2.53-2.55

(m, 1H), 2.33-2.40 (m, 4H), 1.85 (s, 3H), 1.35-1.80 (m, 9H), 1.30-1.33 (m, 1H); RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 13.29 min.;
MS: MH^+ 444

Example 800: *Cis N*1-(4-{4-amino-1-[4-(2-amino-2-oxoethyl)-4-hydroxycyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(*trans*)-2-phenyl-1-cyclopropanecarboxamide

To a well-stirred solution of *cis N*1-(4-{4-amino-1-[4-(cyanomethyl)-4-hydroxycyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(*trans*)-2-phenyl-1-cyclopropanecarboxamide (0.200 g, 0.00037 mol) in dimethylsulfoxide (4 mL) potassium carbonate (0.216 g, 0.00156 mol) was added at ambient temperature. A 30% aqueous solution of hydrogen peroxide (0.6 mL) was added dropwise, keeping the temperature constant. The mixture was stirred at ambient temperature for 32 hours. Water (20 mL) was added to the mixture, and the precipitate which formed was filtered. The precipitate was washed with water and dried *in vacuo*. The solid was purified by preparative RP-HPLC (Rainin C18, 8μm, 300 A, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M ammonium acetate over 15 min, 21 ml/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyopholyzed to give *cis N*1-(4-{4-amino-1-[4-(2-amino-2-oxoethyl)-4-hydroxycyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(*trans*)-2-phenyl-1-cyclopropanecarboxamide as a white solid (0.117 g, 0.00021 mol):
^{1}H NMR (DMSO-d_6, 400MHz) δ 9.64 (s, 1H), 8.23 (d, 1H), 8.22 (s, 1H), 7.43-7.48 (m, 1H), 7.15-7.35 (m, 7H), 7.05-7.10 (m, 1H), 4.97 (s, 1H), 4.61-4.71 (m, 1H), 3.91 (s, 3H), 2.54-2.64 (m, 1H), 2.30-2.44 (m, 3H), 2.24 (s, 2H), 1.55-1.81 (m, 6H), 1.45-1.53 (m, 1H), 1.28-1.36 (m, 1H);
RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 14.05 min.;
MS: MH^+ 556.

Example 801: Cis *N*1-[4-(4-amino-1-{4-[(dimethylamino)methyl]-4-

hydroxycyclohexyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-(*trans*)-2-phenyl-1-cyclopropanecarboxamide acetate

To a solution of *cis N*1-{4-[4-amino-1-(1-oxaspiro[2.5]oct-6-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-(*trans*)-2-phenylcyclopropane-1-carboxamide (0.190 g, 0.000302 mol) in 2-propanol (10 mL) a 2 M solution of dimethylamine in methanol (0.91 mL) was added and the resulting mixture was heated at 65° C in a pressure tube for 18 hours. The solvent was removed *in vacuo,* and the residue was purified by preparative RP-HPLC (Rainin C18, 8μm, 300 A, 25 cm; 30% isocratic for five minutes, then 30%-60% acetonitrile - 0.1M ammonium acetate over 15 min, 21 ml/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyopholyzed to give Cis *N*1-[4-(4-amino-1-{4-[(dimethylamino)methyl]-4-hydroxycyclohexyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-(*trans*)-2-phenyl-1-cyclopropanecarboxamide acetate as a white solid (0.109 g, 0.000177 mol).:

^{1}H NMR (DMSO-d_6, 400MHz) δ 9.64 (s, 1H), 8.23 (d, 1H), 8.22-8.24 (m, 1H), 7.17-7.33 (m, 7H), 4.56-4.68 (m, 1H), 3.91 (s, 3H), 2.54-2.64 (m, 1H), 2.30-2.44 (m, 3H), 2.28 (s, 6H), 2.24 (s, 2H), 1.91 (s, 3H), 1.63-1.78 (m, 4H), 1.44-1.58 (m, 3H), 1.28-1.36 (m, 1H); RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 13.54 min.;

MS: MH^+ 556.

Example 802: *Trans N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(2*R*)tetrahydro-1*H*-2-pyrrolecarboxamide acetate

A solution of *trans* 3-(4-amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.200 g, 0.00046 mol) in *N,N*-dimethylformamide (10 mL) was reacted with 1-hydroxy-7-azabenzotriazole (0.068 g, 0.00050 mol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.132 g, 0.00069 mol), D-Boc-proline (0.108 g, 0.00050 mol) and *N,N*-diisopropylethylamine (0.184 g, 0.00142 mol) at ambient temperature for 24 hours. The solvent was removed *in vacuo* and the residue was

partitioned between dichloromethane (10 mL) and a 5% aqueous citric acid solution (20 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 10 mL). The combined organic phases were washed with saturated aqueous sodium bicarbonate (15 mL) and dried over magnesium sulfate. The solvent was removed *in vacuo* and the residue was stirred in 20% trifluoroacetic acid in dichloromethane for 6 hours at ambient temperature. The solvent was removed *in vacuo* and the residue was purified by preparative RP-HPLC (Rainin C18, 8mm, 300 A, 25 cm; 5% isocratic for five minutes, then 5%-40% acetonitrile - 0.1M ammonium acetate over 20 min, 21 ml/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyopholyzed to give *trans N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-(2*R*)tetrahydro-1*H*-2-pyrrolecarboxamide acetate (0.096 g, 0.00016 mol) as a white solid.

^{1}H NMR (DMSO-d_6, 400MHz) δ 10.33 (s, 1H), 8.45 (d, 1H), 8.22 (s, 1H), 7.25 (s, 1H), 7.21 (d, 1H), 4.58-4.69 (m, 1H), 3.93 (s, 3H), 3.77 (dd, 1H), 2.96-3.04 (m, 1H), 2.74-2.84 (m, 1H), 2.47-2.58 (m, 5H), 2.23-2.45 (m, 5H), 2.14 (s, 3H), 1.91 (s, 3H), 1.88-2.11 (m, 7H), 1.78-1.88 (m, 1H), 1.60-1.69 (m, 2H), 1.39-1.54 (m, 2H);
RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 8.47 min.;
MS: MH^+ 534.

Example 803: 4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-pyridiniumolate

A. 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-pyridiniumolate

A solution of 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (5.00 g, 0.019 mol) in *N,N*-dimethylformamide (50 mL) was reacted with 60% sodium hydride in oil (0.92 g, 0.023 mol) at ambient temperature. The mixture was stirred for 15 minutes, and 4-nitropyridine-*N*-oxide (5.37 g, 0.038 mol) was added. The mixture was heated at 100° C. for 18 hours. The precipitate which formed was filtered, washing with *N,N*-dimethylformamide and ethyl acetate to give 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-pyridiniumolate (3.79 g, 0.011 mol) as a tan solid:

^{1}H NMR (DMSO-d_6, 400MHz) δ 8.38 (s, 1H), 8.34 (d, 2H), 8.24 (d, 2H);
RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) R_t 7.36 min.;
MS: MH^+ 355.

B. 4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-pyridiniumolate

A suspension of 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-d]pyrimidin-1-yl)-1-pyridiniumolate (0.140 g, 0.00040 mol) in dimethoxyethane (7 mL) and water (15 mL) was reacted with 4-phenoxyphenylboronic acid (0.093 g, 0.00043 mol), sodium carbonate (0.105 g, 0.00099 mol) and tetrakis(triphenylphosphine) palladium (0) (0.046 g, 0.00004 mol) at 80° C for 18 hours. The solid was filtered to give 4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-pyridiniumolate (0.138 g, 0.00035 mol) as a brown solid. A portion (0.040 g, 0.00010 mol) was purified by preparative RP-HPLC (Rainin C18, 8μm, 300 A, 25 cm; 40% isocratic for five minutes, then 40%-100% acetonitrile - 0.1M ammonium acetate over 30 min, 21 ml/min). The acetonitrile was removed *in vacuo* and the aqueous mixture was lyopholyzed to give the product 4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-pyridiniumolate as a white solid (0.013 g, 0.00003 mol).
^{1}H NMR (DMSO-d_6, 400MHz) δ 8.44 (s, 1H), 8.34-8.41 (m, 4H), 7.77 (d, 2H), 7.45 (t, 2H), 7.13-7.24 (m, 5H);
RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 14.66 min.;
MS: MH^+ 397.

Example 804: 3-(4-phenoxyphenyl)-1-(4-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

A suspension of 4-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-pyridiniumolate (0.100 g, 0.00025 mol) and 10% palladium on carbon (0.016 g, 0.00002 mol) in acetic acid (3 mL) was reacted with sodium hypophosphite monohydrate (0.033 g, 0.00038 mol) at 60° C. After 2 hours, an

additional 10% palladium on carbon (0.016 g, 0.00002 mol) was added. The mixture was stirred 18 hours after which time additional 10% palladium on carbon (0.016 g, 0.00002 mol) and sodium hypophosphite monohydrate (0.033 g, 0.00038 mol) was added. The mixture was stirred for an additional 24 hours. The mixture was filtered through Celite ® 521, washing with acetic acid. The solvent was removed *in vacuo*, and the residue was purified by preparative RP-HPLC (Rainin C18, 8mm, 300 A, 25 cm; 40% isocratic for five minutes, then 40%-100% acetonitrile - 0.1M ammonium acetate over 30 min, 21 ml/min). The acetonitrile was removed in vacuo and the aqueous mixture was lyopholyzed to give 3-(4-phenoxyphenyl)-1-(4-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.020 g, 0.00005 mol) as a white solid:
^{1}H NMR (DMSO-d_6, 400MHz) δ 8.71 (d, 2H), 8.46 (s, 1H), 8.39 (dd, 2H), 7.78 (d, 2H), 7.46 (t,2H), 7.13-7.25 (m, 5H);
RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 17.31 min.;
MS: MH^+ 381.

Example 805: *N*2-{4-[4-amino-1-(4-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide

A. *N*2-{4-[4-amino-1-(4-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide

A suspension of 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-d]pyrimidin-1-yl)-1-pyridiniumolate (0.500 g, 0.0014 mol) in dimethoxyethane (15 mL) and water (30 mL) was reacted with *N*2-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-methyl-1*H*-2-indolecarboxamide (0.631 g, 0.00155 mol), sodium carbonate (0.374 g, 0.0035 mol) and tetrakis(triphenylphosphine) palladium (0) (0.163 g, 0.00014 mol) at 80° C for 18 hours. The solid was filtered and washed with water. The solid was slurried in ethyl acetate for 18 hours and filtered, washing with ethyl acetate. The solid was dried *in vacuo* to give crude 4-[4-amino-3-(3-methoxy-4-[(1-methyl-1*H*-2-indolyl)-carbonyl]aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-pyridiniumolate (0.523 g, 0.0010 mol) as a brown solid:
RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) R_t 10.92 min.;

MS: MH^+ 507.

B. *N*2-{4-[4-amino-1-(4-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide

A suspension of 4-[4-amino-3-(3-methoxy-4-{[(1-methyl-1*H*-2-indolyl)carbonyl]amino} phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-pyridiniumolate (0.200 g, 0.00039 mol) and 10% palladium on carbon (0.042 g, 0.00004 mol) in acetic acid (3 mL) was reacted with sodium hypophosphite monohydrate (0.063 g, 0.00059 mol) at 60° C for 2 hours. Additional 10% palladium on carbon (0.042 g, 0.00004 mol) and sodium hypophosphite (0.045 g, 0.00042 mol) was added and the mixture was stirred for 24 hours. The solvent was removed *in vacuo* and the residue was slurried in methanol for 4 hours. The mixture was filtered through Celite ® 521, washing with methanol. The solvent was removed *in vacuo* and the residue was purified by preparative RP-HPLC (Rainin C18, 8mm, 300 A, 25 cm; 50% isocratic for five minutes, then 50%-100% acetonitrile - 0.1M ammonium acetate over 25 min, 21 ml/min). The acetonitrile was removed in vacuo and the aqueous mixture was lyopholyzed to give *N*2-{4-[4-amino-1-(4-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide (0.020 g, 0.00004 mol) as a white solid:

^{1}H NMR (DMSO-d_6, 400MHz) δ 9.48 (s, 1H) 8.72 (d, 2H), 8.47 (s, 1H), 8.42 (d, 2H), 8.20 (d, 1H), 7.72 (d, 1H), 7.60 (d, 1H), 7.48 (s, 1H), 7.42 (d, 1H), 7.36 (s, 1H) 7.34 (t, 1H), 7.16 (t, 1H), 4.05 (s, 3H), 3.99 (s, 1H);

RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 19.50 min.;

MS: MH^+ 491.

Example 806: 1-(6-amino-3-pyridyl)-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine; and

Example 807: 3-(4-phenoxyphenyl)-1-(2-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

A solution of 3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine (0.200 g, 0.00079 mol) in N-methyl pyrrolidinone (10 mL) was reacted with 60% sodium hydride in oil (0.032 g, 0.00079 mol). After gas evolution ceased, the

mixture was stirred at ambient temperature for 30 minutes, and 5-bromo-2-nitropyridine (0.161 g, 0.00079 mol) was added and heated at 40° C for 18 hours. Additional 60% sodium hydride in oil (0.032 g, 0.00079 mol) was added and the mixture was stirred an additional 2 hours. The solvent was removed *in vacuo* and the residue was partitioned between dichloromethane (15 mL) and water (25 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 15 mL). The combined organics were washed with brine and dried over magnesium sulfate. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica using heptane/ethyl acetate (1:2) as an eluent to give two products. The less polar compound, 1-(6-nitro-3-pyridyl)-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine, was suspended in absolute ethanol (10 mL) and *N,N*-dimethylformamide (5 mL) and 10% palladium on carbon (0.007 g) was added. The mixture was stirred under a balloon atmosphere of hydrogen for 18 hours. The mixture was filtered through pad of Celite ® 521, washing with absolute ethanol. The solvent was removed *in vacuo* to give 1-(6-amino-3-pyridyl)-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.007 g, 0.00002 mol) as a white solid.

^{1}H NMR (DMSO-d_6, 400MHz) δ 8.53 (d, 1H) 8.31 (s, 1H), 7.97 (dd, 1H), 7.73 (d, 2H), 7.44 (t, 2H), 7.12-23 (m, 5H), 6.60 (d, 1H), 6.20 (s, 2H); RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 15.38 min.; MS: MH^+ 396.

The more polar compound, 3-(4-phenoxyphenyl)-1-(5-bromo-2-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine, was suspended in absolute ethanol (10 mL) and *N,N*-dimethylformamide (5 mL) and 10% palladium on carbon (0.007 g) was added. The mixture was stirred under a balloon atmosphere of hydrogen for 18 hours. The mixture was filtered through pad of Celite ® 521, washing with absolute ethanol. The solvent was removed *in vacuo* to give 3-(4-phenoxyphenyl)-1-(2-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.030 g, 0.00007 mol) as a white solid.

^{1}H NMR (DMSO-d_6, 400MHz) δ 8.60-8.64 (m, 1H) 8.37 (s, 1H), 8.20 (d, 1H), 8.03-8.08 (m, 1H), 7.76 (d, 2H), 7.41-7.49 (m, 3H), 7.12-7.23 (m, 5H);

RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 16.32 min.;

MS: MH^+ 381.

A general procedure for reductive amination with *trans*-3-(4-amino-phenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine and an aldehyde as starting materials is given below. Examples 808 and 809 were prepared using this method.

Protocol:

A mixture of *trans*-3-(4-amino-phenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (1 eq.), the corresponding aldehyde (1.05 eq.), sodium triacetoxyborohydride (3.4 eq.) and acetic acid (3.4 eq) was stirred in anhydrous 1,2-dichloroethane for 16 hours. The reaction mixture was concentrated under reduced pressure, quenched with saturated solution of sodium bicarbonate in water and concentrated again. The residue was purified by preparative HPLC (Hypersil C18, 8μm, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield the desired products. Example 808 was prepare according to this method using the aldehyde 2-methoxy-3-formyl-pyridine and Example 809 was prepared using the aldehyde 2-formy-indole.

Example 808: *trans*-3-(4-[(2-methoxy-3-pyridyl)methyl]aminophenyl)-1-[4-(4-methyl-piperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

^{1}H NMR (DMSO-d_6, 400MHz) δ 8.18 (s, 1H), 8.06 (dd, 1H), 7.61 (d, 1H), 7.35 (d, 2H), 6.95 (dd, 1H), 6.69 (d, 2H), 6.51 (t, 1H), 4.60 (m, 1H), 4.26 (d, 2H), 3.94 (s, 3H), 2.64 (s, 3H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 6H), 1.46 (m, 2H); RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 12.07 min.
MS: MH^+ 528.

Example 809: *trans*-3-{4-[(1*H*-2-indolylmethyl)amino]phenyl}-1-[4-(4-methylpiperazino)-cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

^{1}H NMR (DMSO-d_6, 400MHz) δ 11.08 (s, 1H), 8.19 (s, 1H), 7.44 (d, 1H), 7.36 (d, 2H), 7.32 (d, 1H), 7.01 (t, 1H), 6.95 (t, 1H), 6.81 (d, 2H), 6.47 (t, 1H), 6.35 (s, 1H), 4.60 (m, 1H), 4.45 (d, 2H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H);

RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 13.74 min.

MS: MH^+ 536.

Example 810: *Trans*-3-[(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)methyl]-1,2-dihydro-2-pyridinone diacetate

Trans-3-(4-[(2-methoxy-3-pyridyl)methyl]aminophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-d]pyrimidin-4-amine diacetate (0.105 g, 0.000199mol) was dissolved in 30% hydrogen bromide in acetic acid (4 mL) and the mixture was refluxed for 1.5 hours. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC (Hypersil C18, 8μm, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield *trans*-3-[(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-d]pyrimidin-3-yl}anilino)methyl]-1,2-dihydro-2-pyridinone diacetate (0.0204 g, 0.0000324 mol) as a white solid.

^{1}H NMR (DMSO-d_6, 400MHz) δ 8.18 (s, 1H), 7.29 (m, 4H), 6.68 (d, 2H), 6.40 (t, 1H), 6.15 (m, 1H), 4.60 (m, 1H), 4.09 (d, 2H), 2.64 (s, 3H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 6H), 1.46 (m, 2H);

RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 9.40 min. MS: MH^+ 514.

A general procedure for reductive amination with *trans*-3-(4-amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine and an aldehyde as starting materials is given below. Examples 811-813 were prepared using this method.

Protocol :

A mixture of *trans*-3-(4-amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4- (1 eq.), the corresponding aldehyde (1.05 eq.), sodium triacetoxyborohydride (3.4 eq.) and acetic acid (3.4 eq) was stirred in anhydrous 1,2-dichloroethane for 16 hours. The reaction mixture was concentrated under reduced pressure, quenched with saturated solution of sodium bicarbonate in water and concentrated again. The residue was purified by preparative HPLC (Hypersil C18, 8μm, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield the desired products.

Example 811 was prepared using the aldehyde 2-amino-4-chloro-5-formyl-1,3-thiazole. Example 812 was prepared using the aldehyde 5-methyl-3-formyl-isoxazole. Example 813 was prepared using the aldehyde 4-formy-1,3-thiazole.

Example 811: *Trans*-5-[(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyanilino)methyl]-4-chloro-1,3-thiazol-2-amine diacetate

^{1}H NMR (DMSO-d_6, 400MHz) δ 8.19 (s, 1H), 7.19 (s, 2H), 7.06 (m, 3H), 6.68 (d, 1H), 5.76 (t, 1H), 4.60 (m, 1H), 4.30 (d, 2H), 3.85 (s, 3H), 2.6-2.2 (br, 9H), 2.17 (s, 3H), 2.05 (m, 6H), 1.91 (s, 6H), 1.46 (m, 2H);

RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 11.59 min.

MS: MH^+ 583.

Example 812: *Trans*-3-(3-methoxy-4-[(5-methyl-3-isoxazolyl)methyl]aminophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

^{1}H NMR (DMSO-d_6, 400MHz) δ 8.19 (s, 1H), 7.04 (m, 2H), 6.68 (d, 1H), 6.16 (s, 1H), 5.86 (t, 1H), 4.60 (m, 1H), 4.37 (d, 2H), 3.86 (s, 3H), 2.6-2.2 (br, 9H), 2.40 (s, 3H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H);

RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 11.53 min.

MS: MH^+ 532.

Example 813: *Trans*-3-{3-methoxy-4-[(1,3-thiazol-4-ylmethyl)amino]phenyl}-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

^{1}H NMR (DMSO-d_6, 400MHz) δ 9.08 (s, 1H), 8.19 (s, 1H), 7.47 (s, 1H), 7.06 (s, 1H), 7.03 (d, 1H), 6.68 (d, 1H), 5.76 (t, 1H), 4.60 (m, 1H), 4.52 (d, 2H), 3.88 (s, 3H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H);
RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 11.17 min.
MS: MH^+ 534.

A general procedure for the synthesis of benzotetrahydrofuran-derivatives with *trans*- 3-(4-aminophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-d]pyrimidin-4-amine and the appropriate 2-hydroxy-benzaldehdye as starting material is given below. Examples 814 and 815 were prepared using this method.

Protocol:

Trans-3-(4-aminophenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-d]pyrimidin-4-amine (1 equiv., 0.0001–0.0002 mol scale) and the corresponding 2-hydroxy-benzaldehdye (1 equiv.) were combined in absolute ethanol (5 mL) and stirred at ambient temperature for 48 hours. The reaction mixture was concentrated under reduced pressure and the residue dried overnight to yield the corresponding imine, which was used without further purification. Trimethylsulfoxonium iodide (2.5 equiv.) was dissolved in anhydrous dimethylsulfoxide (2 mL) and a 60% dispersion of sodium hydride in parafine (2.5 equiv.) was added at once. After 10 min., the solution of the imine in anhydrous dimethylsulfoxide (2 mL) was added and the resulting mixture was stirred at ambient temperature under an atmosphere of nitrogen for 2.5 hours. The solution was poured into ice-cold water (50 mL) and extracted with dichloromethane (2x40 mL). The combined organic extracts were dried with magnesium sulfate and concentrated under reduced pressure. The residue was purified by preparative HPLC (Hypersil C18, 8μm, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25

min, 21mL/min) to yield the final compound.

Example 814 was prepared using 2-hydroxy-4,6-dichlorobenzaldehyde and Example 815 was prepared using 2-hydroxy-4-chlorobenzaldehyde.

Example 814: *Trans*-3-4-[(4,6-dichloro-2,3-dihydrobenzo[*b*]furan-3-yl)amino]phenyl-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

^{1}H NMR (DMSO-d_6, 400MHz) δ 8.19 (s, 1H), 7.39 (d, 2H), 7.14 (s, 1H), 7.07 (s, 1H), 6.80 (d, 2H), 6.56 (d, 1H), 5.34 (m, 1H), 4.80 (dd, 1H), 4.60 (m, 1H), 4.42 (dd, 1H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H);
RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 16.03 min.
MS: MH^+ 593.

Example 815: *Trans*-3-{4-[(4-chloro-2,3-dihydrobenzo[*b*]furan-3-yl)amino]phenyl}-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

^{1}H NMR (DMSO-d_6, 400MHz) δ 8.20 (s, 1H), 7.39 (d, 2H), 7.28 (t, 1H), 6.99 (d, 1H), 6.89 (d, 1H), 6.81 (d, 2H), 6.53 (d, 1H), 5.34 (m, 1H), 4.74 (dd, 1H), 4.60 (m, 1H), 4.38 (dd, 1H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H);
RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 14.42 min.
MS: MH^+ 559.

Example 816: *Trans*-3-4-[(4,6-dichloro-2,3-dihydrobenzo[b]furan-3-yl)amino]-3-methoxyphenyl-1-[4-(4-methylpiperazino) cyclohexyl]-1*H*-pyrazolo[3,4-d]pyrimidin-4-amine acetate

Trans-3-4-[(4,6-dichloro-2,3-dihydrobenzo[b]furan-3-yl)amino]-3-methoxyphenyl-1-[4-(4-methylpiperazino) cyclohexyl]-1*H*-pyrazolo[3,4-d]pyrimidin-4-amine acetate was prepared using the method of Examples 814 and 815 using *trans*- 3-(4-amino-3-methoxyphenyl)-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-d]pyrimidin-4-amine and 2-hydroxy-

4,6-dichlorobenzaldehyde as the starting materials.

^{1}H NMR (DMSO-d_6, 400MHz) δ 8.20 (s, 1H), 7.11 (m, 4H), 6.80 (d, 1H), 5.45(m, 2H), 4.84 (dd, 1H), 4.60 (m, 1H), 4.42 (dd, 1H), 3.82 (s, 3H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H);

RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 16.85 min.

MS: MH^+ 623.

Intermediate 7: *tert*-butyl 4-[4-amino-3-(4-aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate

A. *tert*-butyl 4-[4-amino-3-(4-[(benzyloxy)carbonyl]aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate

A mixture of benzyl *N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (9.54 g, 0.027 mol), *tert*-butyl 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-piperidinecarboxylate (10.0 g, 0.0225 mol), tetrakis-(triphenylphosphine)palladium (1.56 g, 0.00135 mol) and sodium carbonate (5.97 g, 0.0563 mol) was heated in a mixture of ethylene glycol dimethyl ether (120 mL) and water (60 mL) at 80° C for 16 hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature and solvents were removed under the reduced pressure. The residue was partitioned between water (150 mL) and dichloromethane (150 mL); the organic phase was washed with brine, dried with magnesium sulfate and concentrated under reduced pressure. The residue was triturated in diethyl ether and the precipitate was collected by filtration and dried to yield *tert*-butyl 4-[4-amino-3-(4-[(benzyloxy)carbonyl]aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate (10.1 g, 0.0186 mol) as a white solid.

^{1}H NMR (DMSO-d_6, 400MHz) δ 10.00 (s, 1H), 8.23 (s, 1H), 7.64 (d, 2H), 7.43 (d, 2H), 7.36 (m, 5H), 5.18 (s, 2H), 4.90 (m, 1H), 4.08 (br, 2H), 3.00 (br, 2H), 2.02 (m, 4H), 1.42 (s, 9H);

RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 18.58 min.

B. *tert*-butyl 4-[4-amino-3-(4-aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate

To a solution of *tert*-butyl 4-[4-amino-3-(4-[(benzyloxy)carbonyl]aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate (5.0 g, 0.0092 mol) in terahydrofuran (150 mL) 10% palladium on carbon (1.0 g) was added and the reaction mixture was hydrogenated on a Parr shaker over 96 hours. The catalyst was removed by filtration through a Celite pad and the filtrate was concentrated under reduced pressure. The residue was triturated in n-heptane and the precipitate was collected by filtration and dried to yield *tert*-butyl 4-[4-amino-3-(4-aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate (2.51 g, 0.0061 mol) as an off-white solid.
^{1}H NMR (DMSO-d_6, 400MHz) δ 8.20 (s, 1H), 7.35 (d, 2H), 6.69 (d, 2H), 5.42 (s, 2H), 4.90 (m, 1H), 4.08 (br, 2H), 3.00 (br, 2H), 2.02 (m, 4H), 1.42 (s, 9H);
RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 14.18 min.

Examples 817-829 were prepared with the following general procedure for reductive amination followed by BOC deprotection. *Tert*-butyl 4-[4-amino-3-(4-aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate and the appropriate aldehydre were used as starting materials.

Protocol:

A mixture of *tert*-butyl 4-[4-amino-3-(4-aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate (1 eq.), aldehyde (1.2 eq.), sodium triacetoxyborohydride (3.4 eq.) and acetic acid (3.4 eq) was stirred in anhydrous 1,2-dichloroethane for 16 hours. The reaction mixture was concentrated under reduced pressure, triturated in ethyl acetate and treated with with a 4N aqueous solution of hydrochloric acid.. The resulting mixture was stirred for 1 hour; aqueous phase was neutralized with saturated solution of sodium bicarbonate in water and the layers separated. Organic phase was concentrated under reduced pressure and the residue was purified by preparative HPLC (Hypersil C18, 8μm, 25 cm; 10-60% acetonitrile

– 0.1M ammonium acetate over 25 min, 21mL/min) to yield the desired products. The following compounds were made using the above procedure:

Example 817: 3-{4-[(benzo[*b*]furan-2-ylmethyl)amino]phenyl}-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

^{1}H NMR (DMSO-d_6, 400MHz) δ 8.19 (s, 1H), 7.57 (d, 1H), 7.53 (d, 1H), 7.39 (d, 2H), 7.23 (m, 2H), 6.85 (d, 2H), 6.80 (s, 1H), 6.66 (t, 1H), 4.70 (m, 1H), 4.51 (d, 2H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);
RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 13.37 min.
MS: MH^+ 440.

Example 818: 3-(4-[(2-methoxy-3-pyridyl)methyl]aminophenyl)-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

^{1}H NMR (DMSO-d_6, 400MHz) δ 8.19 (s, 1H), 8.06 (d, 1H), 7.61 (d, 1H), 7.36 (d, 2H), 6.96 (dd, 1H), 6.69 (d, 2H), 6.51 (t, 1H), 4.70 (m, 1H), 4.27 (d, 2H), 3.94 (s, 3H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);
RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 11.06 min.
MS: MH^+ 431.

Example 819: 3-(4-[(5-methyl-2-thienyl)methyl]aminophenyl)-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

^{1}H NMR (DMSO-d_6, 400MHz) δ 8.19 (s, 1H), 7.36 (d, 2H), 6.85 (d, 1H), 6.77 (d, 2H), 6.64 (d, 1H), 6.54 (t, 1H), 4.70 (m, 1H), 4.41 (d, 2H), 3.07 (m, 2H), 2.65 (m, 2H), 2.38 (s, 3H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);
RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 12.85 min.
MS: MH^+ 420.

Example 820: 3-{4-[(2-furylmethyl)amino]phenyl}-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

^{1}H NMR (DMSO-d_6, 400MHz) δ 8.19 (s, 1H), 7.59 (s, 1H), 7.36 (d, 2H), 6.77 (d, 2H), 6.46 (t, 1H), 6.39 (d, 1H), 6.34 (d, 1H), 4.70 (m, 1H), 4.31 (d, 2H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);
RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 10.96 min.
MS: MH^+ 390.

Example 821: 3-[4-(benzylamino)phenyl]-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

^{1}H NMR (DMSO-d_6, 400MHz) δ 8.19 (s, 1H), 7.34 (m, 6H), 7.24 (t, 1H), 6.73 (d, 2H), 6.60 (t, 1H), 4.70 (m, 1H), 4.33 (d, 2H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);
RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 12.32 min.
MS: MH^+ 400.

Example 822: 3-{4-[(2-methoxybenzyl)amino]phenyl}-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

^{1}H NMR (DMSO-d_6, 400MHz) δ 8.19 (s, 1H), 7.35 (d, 2H), 7.24 (m, 2H), 7.01 (d, 1H), 6.90 (t, 1H), 6.70 (d, 2H), 6.41 (t, 1H), 4.70 (m, 1H), 4.28 (d, 2H), 3.85 (s, 3H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);
RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 12.73 min.
MS: MH^+ 430.

Example 823: 3-{4-[(3-methoxybenzyl)amino]phenyl}-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

^{1}H NMR (DMSO-d_6, 400MHz) δ 8.19 (s, 1H), 7.35 (d, 2H), 7.25 (t, 1H), 6.96 (m, 2H), 6.81 (d, 1H), 6.72 (d, 2H), 6.59 (t, 1H), 4.70 (m, 1H), 4.30 (d, 2H), 3.74 (s, 3H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);
RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 12.38 min.

MS: MH^+ 430.

Example 824: 3-{4-[(4-methoxybenzyl)amino]phenyl}-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

^{1}H NMR (DMSO-d_6, 400MHz) δ 8.19 (s, 1H), 7.35 (m, 4H), 6.90 (d, 2H), 6.72 (d, 2H), 6.51 (t, 1H), 4.70 (m, 1H), 4.25 (d, 2H), 3.73 (s, 3H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 12.37 min.

MS: MH^+ 430.

Example 825: 1-(4-piperidyl)-3-(4-[3-(trifluoromethyl)benzyl]aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

^{1}H NMR (DMSO-d_6, 400MHz) δ 8.19 (s, 1H), 7.71 (m, 2H), 7.58 (m, 2H), 7.36 (d, 2H), 6.72 (m, 3H), 4.70 (m, 1H), 4.44 (d, 2H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 14.08 min.

MS: MH^+ 468.

Example 826: 1-(4-piperidyl)-3-(4-[4-(trifluoromethyl)benzyl]aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

^{1}H NMR (DMSO-d_6, 400MHz) δ 8.19 (s, 1H), 7.70 (d, 2H), 7.60 (d, 2H), 7.36 (d, 2H), 6.72 (m, 3H), 4.70 (m, 1H), 4.44 (d, 2H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 14.23 min.

MS: MH^+ 468.

Example 827: 3-(4-[(2-methyl-1,3-thiazol-4-yl)methyl]aminophenyl)-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

^{1}H NMR (DMSO-d_6, 400MHz) δ 8.19 (s, 1H), 7.41 (d, 2H), 7.26 (s, 1H), 6.73 (d,

2H), 6.51 (t, 1H), 4.70 (m, 1H), 4.36 (d, 2H), 3.07 (m, 2H), 2.70 (s, 3H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 10.13 min.

MS: MH^+ 421.

Example 828: 3-{4-[(2-chloro-6-fluorobenzyl)amino]phenyl}-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

^{1}H NMR (DMSO-d_6, 400MHz) δ 8.19 (s, 1H), 7.42 (m, 4H), 7.26 (t, 1H), 6.83 (d, 2H), 6.27 (t, 1H), 4.72 (m, 1H), 4.37 (d, 2H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 12.32 min.

MS: MH^+ 452.

Example 829: 3-(4-[2-fluoro-4-(trifluoromethyl)benzyl]aminophenyl)-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

^{1}H NMR (DMSO-d_6, 400MHz) δ 8.19 (s, 1H), 7.61 (m, 3H), 7.38 (d, 2H), 6.73 (d, 2H), 6.68 (t, 1H), 4.70 (m, 1H), 4.47 (d, 2H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 12.83 min.

MS: MH^+ 486.

Example 830: 3-{4-[(benzo[*b*]furan-2-ylmethyl)amino]-3-methoxyphenyl}-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate

A mixture of *tert*-butyl 4-[4-amino-3-(4-amino-3-methoxyphenyl)-1*H*-pyrazolo[3,4-d]pyrimidin-1-yl]-1-piperidinecarboxylate (g, mol), benzofuran-2-carbaldehyde (0.046 g, 0.000315 mol), sodium triacetoxyborohydride (0.089 g, 0.00042 mol.) and acetic acid (0.024 mL, 0.00042 mol) was stirred in anhydrous 1,2-dichloroethane for 16 hours. The reaction mixture was concentrated under reduced pressure, triturated in ethyl acetate (4mL) and treated with a 4N aqueous solution of

hydrochloric acid (1 mL). The resulting mixture was stirred for 1 hour; aqueous phase was neutralized with saturated solution of sodium bicarbonate in water and the layers separated. The organic phase was concentrated under reduced pressure and the residue was purified by preparative HPLC (Hypersil C18, 8μm, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield 3-{4-[(benzo[*b*]furan-2-ylmethyl)amino]-3-methoxyphenyl}-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine diacetate (0.027 g, 0.0000457 mol).
^{1}H NMR (DMSO-d_6, 400MHz) δ 8.19 (s, 1H), 7.55 (m, 2H), 7.22 (m, 2H), 7.06 (m, 2H), 6.80 (d, 1H), 6.75 (s, 1H), 5.80 (t, 1H), 4.70 (m, 1H), 4.57 (d, 2H), 3.89 (s, 3H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 6H), 1.79 (m, 2H);
RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 14.83 min.
MS: MH^+ 470.

Example 831: 3-[4-(2,3-dihydrobenzo[*b*]furan-3-ylamino)phenyl]-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

Salicylaldehyde (0.063 g, 0.000513 mol) and *tert*-butyl 4-[4-amino-3-(4-aminophenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate (0.200 g, 0.000489 mol) were combined in absolute ethanol (5 mL) and stirred at ambient temperature for 48 hours. The reaction mixture was concentrated under reduced pressure and the residue dried overnight to yield *tert*-butyl 4-[4-amino-3-(4-{[-1-(2-hydroxyphenyl)methylidene]amino}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate which was used without further purification.
Trimethylsulfoxonium iodide (0.269 g, 0.00122 mol) was dissolved in anhydrous dimethylsulfoxide (2 mL) and a 60% dispersion of sodium hydride in parafine (0.049 g, 0.00122 mol) was added at once. After 10 min., the solution of *tert*-butyl 4-[4-amino-3-(4-{[-1-(2-hydroxyphenyl)methylidene]amino}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate in anhydrous dimethylsulfoxide (2 mL) was added and the resulting mixture was stirred at ambient temperature under an atmosphere of nitrogen for 2.5 hours. The solution was poured into ice-cold water (70 mL) and extracted with dichloromethane (2 x 50 mL). The combined organic extracts were dried with magnesium sulfate and concentrated under reduced pressure

to yield crude *tert*-butyl 4-{4-amino-3-[4-(2,3-dihydrobenzo[b]furan-3-ylamino)phenyl]-1H-pyrazolo[3,4-d]pyrimidin-1-yl}-1-piperidinecarboxylate which was used without further purification. The crude compound was dissolved in ethyl acetate (5 mL)and treated with a 4N aqueous solution of hydrochloric acid (1.5 mL). The resulting emulsion was vigorously stirred for 1 hour; the water layer was neutralized with saturated solution of sodium bicarbonate in water and the layers were separated. The organic phase was concentrated under reduced pressure and residue was purified by preparative HPLC (Hypersil C18, 8μm, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield 3-[4-(2,3-dihydrobenzo[*b*]furan-3-ylamino)phenyl]-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate (0.038g, 0.000078 mol) as a white solid

^{1}H NMR (DMSO-d_6, 400MHz) δ 8.19 (s, 1H), 7.41 (m, 3H), 7.25 (t, 1H), 6.89 (m, 4H), 6.51 (t, 1H), 5.35 (m, 1H), 4.79 (m, 2H), 4.27 (m, 1H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 3H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 11.38 min.

MS: MH^+ 428.

Example 832: *Trans*-3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)-1*H*-1λ^6-benzo[*d*]isothiazole-1,1-dione acetate

A. 3-chloro-1*H*-1λ^6-benzo[*d*]isothiazole-1,1-dione

Saccharin (10.0 g, 0.0546 mol) and phosphorus pentachloride (12.6 g, 0.060mol) were heated at 170°C for 1.5 hours. The reaction mixture was cooled to ambient temperature and suspended in diethyl ether (200 mL). The precipitate was collected by filtration, thoroughly washed with diethyl ether and dried to yield 3-chloro-1*H*-1λ^6-benzo[*d*]isothiazole-1,1-dione (3.7 g, 0.0184 mol) as a white solid which was used without further purification.

MS: MH^+ 202.

B. 3-(4-bromoanilino)-1*H*-1λ^6-benzo[*d*]isothiazole-1,1-dione

To a solution of 3-chloro-1*H*-1λ^6-benzo[*d*]isothiazole-1,1-dione (1.0 g, 0.00496 mol) in acetone (20 mL), 4-bromoaniline (1.71 g, 0.00992 mol) was added at once and the mixture was stirred for 15 min. The mixture was concentrated under reduced pressure and the residue was suspended in water (100 mL). The precipitate was collected by filtration, thoroughly washed with water and dried to yield 3-(4-bromoanilino)-1*H*-1λ^6-benzo[*d*]isothiazole-1,1-dione (1.57 g, 0.00467 mol) as a white solid.

^{1}H NMR (DMSO-d_6, 400MHz) δ 10.93 (s, 1H), 8.47 (d, 1H), 8.09 (d, 1H), 7.93 (m, 4H), 7.69 (d, 2H);

C. 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anilino]-1*H*-1λ^6-benzo[*d*] isothiazole-1,1-dione

A mixture of 3-(4-bromoanilino)-1*H*-1λ^6-benzo[*d*]isothiazole-1,1-dione (1.57 g, 0.00467 mol), diboron pinacol ester (1.43 g, 0.00561 mol), [1.1'-bis(diphenylphosphino) ferrocene]-dichloropalladium (II) complex with dichloromethane (1:1) (0.114 g, 0.00014 mol) and potassium acetate (1.37 g, 0.014 mol) in *N,N*-dimethylformamide (35 mL) was heated at 80° C under an atmosphere of nitrogen for 16 hours. The mixture was allowed to cool to ambient temperature and the solvent was removed under reduced pressure. Dichloromethane (70 mL) was added to the residue and the resulting solid was removed by filtration through a pad of Celite. The filtrate was concentrated to leave a yellow oil that was triturated in diethyl ether to yield 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anilino]-1*H*-1λ^6-benzo[*d*] isothiazole-1,1-dione (1.14 g, 0.00297 mol) as a white solid.

^{1}H NMR (DMSO-d_6, 400MHz) δ 10.92 (br, 1H), 8.51 (d, 1H), 8.08 (d, 1H), 7.91 (m, 4H), 7.68 (d, 2H), 1.29 (s, 12H).

D. *Trans*-3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)-1*H*-1λ^6-benzo[*d*]isothiazole-1,1-dione acetate

A mixture of 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anilino]-1*H*-1λ^6-benzo[*d*] isothiazole-1,1-dione (0.09 g, 0.000234 mol), *trans*-3-iodo-1-[4-(4-methylpiperazino)-cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.08 g,

0.00018 mol), tetrakis-(triphenylphosphine)palladium (0.013 g, 0.000011 mol) and sodium carbonate (0.048 g, 0.00045 mol) was heated in a mixture of ethylene glycol dimethyl ether (4 mL) and water (2 mL) at 80° C for 16 hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature and solvents were removed under the reduced pressure. The residue was purified by preparative HPLC (Hypersil C18, 8μm, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield *trans*-3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)-1*H*-1λ^6-benzo[*d*]isothiazole-1,1-dione acetate (0.075 g, 0.000119 mol) as a white solid.

^{1}H NMR (DMSO-d_6, 400MHz) δ 8.29 (d, 1H), 8.23 (s, 1H), 7.91 (m, 3H), 7.79 (m, 2H), 7.66 (d, 2H), 4.65 (m, 1H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H);

RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 11.27 min.

MS: MH^+ 572.

Example 833: *Cis*--3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)-1*H*-1λ^6-benzo[*d*]isothiazole-1,1-dione diacetate

Cis-3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)-1*H*-1λ^6-benzo[*d*]isothiazole-1,1-dione diacetate was prepared from 3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anilino]-1*H*-1λ^6-benzo[*d*] isothiazole-1,1-dione (0.09 g, 0.000234 mol) and *cis*-3-iodo-1-[4-(4-methylpiperazino)-cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine by a similar protocol as described above.

^{1}H NMR (DMSO-d_6, 400MHz) δ 8.42 (d, 1H), 8.23 (s, 1H), 7.91 (m, 3H), 7.84 (m, 2H), 7.62 (d, 2H), 4.80 (m, 1H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.07 (m, 4H), 1.91 (s, 6H), 1.65(m, 2H), 1.58 (m, 2H);

RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 11.59 min.

MS: MH^+ 572.

Example 835: *Trans*-*N*3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)benzo[*d*]isoxazol-3-amine acetate

A. *N*1-(4-bromophenyl)-2-fluorobenzamide

A solution of 2-fluorobenzoyl chloride (5.82 g, 0.0367 mol) and 4-bromoaniline (6.31 g, 0.0367 mol) in anhydrous dichloromethane (150 mL) was cooled to 0°C and *N,N*-diisopropylethylamine (5.21 g, 0.0407 mol) was added under nitrogen atmosphere dropwise. The resulting mixture was stirred at ambient temperature for 24 hours, concentrated and the residue partitioned between ethyl acetate (120 mL) and water (100 mL). The organic phase was washed with brine, dried with magnesium sulfate and concentrated. The residue was suspended in cold diethyl ether (50 mL) and the precipitate was collected by filtration and dried to yield *N*1-(4-bromophenyl)-2-fluorobenzamide (9.6 g, 0.0326 mol) as a white solid.

^{1}H NMR (DMSO-d_6, 400MHz) δ 10.54 (s, 1H), 7.66 (m, 3H), 7.56 (m, 3H), 7.34 (m, 2H).

TLC (ethyl acetate / heptane 1:2) R_f 0.37

B. *N*1-(4-bromophenyl)-2-fluoro-1-benzenecarbothioamide

A mixture of *N*1-(4-bromophenyl)-2-fluorobenzamide (3.3 g, 0.0112 mol) and 2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (2.27 g, 0.00561 mol) was heated in toluene at reflux under an atmosphere of nitrogen for 3 hours. The reaction mixture was cooled to ambient temperature, the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica using ethyl acetate/n-heptane (1:6) as mobile phase to yield *N*1-(4-bromophenyl)-2-fluoro-1-benzenecarbothioamide (3.1 g, 0.010 mol) as a yellow solid.

^{1}H NMR (DMSO-d_6, 400MHz) δ 12.13 (s, 1H), 7.93 (d, 2H), 7.62 (m, 3H), 7.51 (m, 1H), 7.31 (m, 2H).

TLC (ethyl acetate / heptane 1:4) R_f 0.27

C. *N*1-(4-bromophenyl)-2-fluoro-1-benzeneamidoxime

A mixture of *N*1-(4-bromophenyl)-2-fluoro-1-benzenecarbothioamide (1.56

g, 0.00505 mol), hydroxylamine hydrochloride (0.44 g, 0.00631 mol) and sodium bicarbonate (0.53 g, 0.00631 mol) was heated in absolute ethanol (25 mL) at reflux under nitrogen atmosphere for 14 hours. The reaction mixture was cooled to ambient temperature, the solvent was removed under reduced pressure and the residue partitioned between saturated solution of sodium bicarbonate in water (50 mL) and ethyl acetate (50 mL). The organic phase was washed with brine, dried with magnesium sulfate and concentrated. The residue was suspended in cold diethyl ether and the precipitate was collected by filtration and dried to yield *N*1-(4-bromophenyl)-2-fluoro-1-benzeneamidoxime (1.21 g, 0.00392 mol) as an off-white solid.

TLC (ethyl acetate / heptane 1:4) R_f 0.12

D. *N*-benzo[*d*]isoxazol-3-yl-*N*-(4-bromophenyl)amine

To a solution of *N*1-(4-bromophenyl)-2-fluoro-1-benzeneamidoxime (1.51 g, 0.00489 mol) in *N*-methylpyrrolidinone (25 mL), potassium *tert*-butoxide (0.54 g, 0.00513 mol) was added and the resulting solution was heated at 100°C under an atmosphere of nitrogen for 3 hours. The reaction mixture was cooled to ambient temperature, the solvent was removed under reduced pressure and the residue partitioned between saturated solution of sodium bicarbonate in water (50 mL) and ethyl acetate (50 mL). The organic phase was washed with brine, dried with magnesium sulfate and concentrated. The residue was purified by flash chromatography on silica using ethyl acetate/ n-heptane (1:5) as mobile phase to yield *N*-benzo[*d*]isoxazol-3-yl-*N*-(4-bromophenyl)amine (0.95 g, 0.00329 mol) as a white solid.

^{1}H NMR (DMSO-d_6, 400MHz) δ 9.72 (s, 1H), 8.13 (d, 1H), 7.68 (d, 2H), 7.61 (m, 2H), 7.54 (d, 2H), 7.37 (dd, 1H).

TLC (ethyl acetate / heptane 1:4) R_f 0.26

E. *N*-benzo[*d*]isoxazol-3-yl-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine

A mixture of *N*-benzo[*d*]isoxazol-3-yl-*N*-(4-bromophenyl)amine (1.30 g, 0.0045 mol), diboron pinacol ester (1.37 g, 0.0054 mol), [1.1'-bis(diphenylphosphino) ferrocene]-dichloropalladium (II) complex with

dichloromethane (1:1) (0.110 g, 0.000135 mol) and potassium acetate (1.32 g, 0.0135 mol) in *N,N*-dimethylformamide (35 mL) was heated at 80° C under an atmosphere of nitrogen for 16 hours. The mixture was allowed to cool to ambient temperature and the solvent was removed under reduced pressure. Dichloromethane (70 mL) was added to the residue and the resulting solid was removed by filtration through a pad of Celite. The filtrate was concentrated to leave a yellow oil that was purified by flash chromatography on silica using ethyl acetate/ n-heptane (1:5) as mobile phase to yield *N*-benzo[*d*]isoxazol-3-yl-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.40 g, 0.00119 mol) as a white solid.

^{1}H NMR (DMSO-d_6, 400MHz) δ 9.74 (s, 1H), 8.16 (d, 1H), 7.70 (m, 4H), 7.61 (d, 2H), 7.37 (dd, 1H), 1.29 (s, 12H).

TLC (ethyl acetate / heptane 1:4) R_f 0.21

F. *Trans-N*3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)benzo[*d*]isoxazol-3-amine acetate

A mixture of *N*-benzo[*d*]isoxazol-3-yl-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.10 g, 0.000298 mol), *trans*-3-iodo-1-[4-(4-methylpiperazino)-cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.101 g, 0.000229 mol), tetrakis-(triphenylphosphine)palladium (0.016 g, 0.0000137 mol) and sodium carbonate (0.061 g, 0.000573 mol) was heated in a mixture of ethylene glycol dimethyl ether (4 mL) and water (2 mL) at 80° C for 16 hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature and solvents were removed under the reduced pressure. The residue was purified by preparative HPLC (Hypersil C18, 8μm, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield *trans-N*3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)benzo[*d*]isoxazol-3-amine acetate (0.102 g, 0.000175 mol) as a white solid.

^{1}H NMR (DMSO-d_6, 400MHz) δ 9.81 (s, 1H), 8.23 (s, 1H), 8.19 (d, 1H), 7.88 (d, 2H), 7.65 (m, 4H), 7.40 (m, 1H), 4.65 (m, 1H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H);

RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium

acetate over 20 min, 1mL/min) R_t 13.66 min.
MS: MH^+ 524.

Example 836: *Cis-N*3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)benzo[*d*]isoxazol-3-amine diacetate

*Cis-N*3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)benzo[*d*]isoxazol-3-amine diacetate was prepared from *N*-benzo[*d*]isoxazol-3-yl-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine and *cis*-3-iodo-1-[4-(4-methylpiperazino)-cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine by a similar protocol as described above.
^{1}H NMR (DMSO-d_6, 400MHz) δ 9.86 (s, 1H), 8.26 (s, 1H), 8.24 (d, 1H), 7.93 (d, 2H), 7.67 (m, 4H), 7.43 (m, 1H), 4.83 (m, 1H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.08 (m, 4H), 1.91 (s, 6H), 1.74 (m, 2H), 1.62 (m, 2H);
RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 13.77 min.
MS: MH^+ 524.

Example 837: *N*3-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}benzo[*d*]isoxazol-3-amine acetate

A mixture of *N*-benzo[*d*]isoxazol-3-yl-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.087 g, 0.000258 mol), *tert*-butyl 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-piperidinecarboxylate (0.088 g, 0.000198 mol), tetrakis-(triphenylphosphine)palladium (0.014 g, 0.000012 mol) and sodium carbonate (0.053 g, 0.000495 mol) was heated in a mixture of ethylene glycol dimethyl ether (4 mL) and water (2 mL) at 80° C for 16 hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature and solvents were removed under the reduced pressure and the residue partitioned between water and dichloromethane. The organic phase was dried with magnesium sulfate and concentrated under reduced pressure to yield crude *tert*-butyl 4-{4-amino-3-[4-(benzo[*d*]isoxazol-3-ylamino)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl}-1-piperidinecarboxylate which was used without further purification.

It was dissolved in ethyl acetate (5 mL) and treated with a 4N aqueous solution of hydrochloric acid (1 mL). The resulting emulsion was vigorously stirred for 1 hour; the water layer was neutralized with saturated solution of sodium bicarbonate in water and the layers were separated. The organic phase was concentrated under reduced pressure and residue was purified by preparative HPLC (Hypersil C18, 8μm, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield *N*3-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}benzo[*d*]isoxazol-3-amine acetate (0.009g, 0,0000185 mol) as a white solid.

^{1}H NMR (DMSO-d_6, 400MHz) δ 9.82 (s, 1H), 8.20 (m, 2H), 7.89 (d, 2H), 7.65 (m, 4H), 7.41 (t, 1H), 4.74 (m, 1H), 3.07 (m, 2H), 2.65 (m, 2H), 2.04 (m, 2H), 1.90 (s, 3H), 1.79 (m, 2H);

RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 11.20 min.

MS: MH^+ 427.

Example 838: *Trans*-3-[4-(1*H*-3-indazolylamino)phenyl]-1-[4-(4-methylpiperazino) cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

A. *N*1-(4-bromophenyl)-2-fluoro-1-benzenecarbohydrazonamide

*N*1-(4-bromophenyl)-2-fluoro-1-benzenecarbothioamide (1.50 g, 0.00485 mol) and a 1M solution of hydrazine in tetrahydrofuran (6.3 mL, 0.0063 mol) were heated in absolute ethanol (25 mL) at reflux under nitrogen atmosphere for 14 hours. Additional 3 mL of a 1M solution of hydrazine in tetrahydrofuran was added and the stirring at reflux was continued for another 6 hours. The reaction mixture was cooled to ambient temperature, the solvent was removed under reduced pressure and the residue partitioned between saturated solution of sodium bicarbonate in water (50 mL) and ethyl acetate (50 mL). The organic phase was washed with brine, dried with magnesium sulfate and concentrated to yield *N*1-(4-bromophenyl)-2-fluoro-1-benzenecarbohydrazonamide (1.54 g, 0.0050 mol) as a tan solid.

TLC (ethyl acetate / heptane 1:3) R_f 0.10

B. *N*-(4-bromophenyl)-*N*-(1*H*-3-indazolyl)amine

To a solution of *N*1-(4-bromophenyl)-2-fluoro-1-benzenecarbohydrazonamide (1.2 g, 0.00391 mol) in *N*-methyl pyrrolidinone (25 mL), potassium *tert*-butoxide (0.50 g, 0.0041 mol) was added and the resulting solution was heated at 100°C under an atmosphere of nitrogen for 3 hours. The reaction mixture was cooled to ambient temperature, the solvent was removed under reduced pressure and the residue partitioned between saturated solution of sodium bicarbonate in water (50 mL) and ethyl acetate (50 mL). The organic phase was washed with brine, dried with magnesium sulfate and concentrated. The residue was purified by flash chromatography on silica using ethyl acetate/ n-heptane (1:5) as mobile phase to yield *N*-(4-bromophenyl)-*N*-(1*H*-3-indazolyl)amine (0.29 g, 0.0010 mol) as a white solid.

^{1}H NMR (DMSO-d_6, 400MHz) δ 12.06 (s, 1H), 9.03 (s, 1H), 7.93 (d, 1H), 7.65 (d, 2H), 7.35 (m, 4H), 7.03 (dd, 1H).

TLC (ethyl acetate / heptane 1:3) R_f 0.26

C. *N*-(1*H*-3-indazolyl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine

A mixture of *N*-(4-bromophenyl)-*N*-(1*H*-3-indazolyl)amine (0.29 g, 0.00101 mol), diboron pinacol ester (0.31 g, 0.00121 mol), [1.1'-bis(diphenylphosphino) ferrocene]-dichloropalladium (II) complex with dichloromethane (1:1) (0.025 g, 0.00003 mol) and potassium acetate (0.294 g, 0.003 mol) in *N,N*-dimethylformamide (35 mL) was heated at 80° C under an atmosphere of nitrogen for 16 hours. The mixture was allowed to cool to ambient temperature and the solvent was removed under reduced pressure. Dichloromethane (70 mL) was added to the residue and the resulting solid was removed by filtration through a pad of Celite. The filtrate was concentrated to leave a yellow oil that was purified by flash chromatography on silica using ethyl acetate/ n-heptane (1:3) as mobile phase to yield *N*-(1*H*-3-indazolyl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.064 g, 0.000191 mol) as an off-white solid.

^{1}H NMR (DMSO-d_6, 400MHz) δ 12.09 (s, 1H), 9.06 (s, 1H), 7.94 (d, 1H), 7.64 (d, 2H), 7.57 (d, 2H), 7.35 (m, 2H), 7.03 (dd, 1H), 1.28 (s, 12H).

TLC (ethyl acetate / heptane 1:3) R_f 0.21

D. *Trans*-3-[4-(1*H*-3-indazolylamino)phenyl]-1-[4-(4-methylpiperazino) cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

A mixture of *N*-(1*H*-3-indazolyl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.064 g, 0.000191 mol), *trans*-3-iodo-1-[4-(4-methylpiperazino)-cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.070 g, 0.000159 mol), tetrakis-(triphenylphosphine)palladium (0.011 g, 0.0000095 mol) and sodium carbonate (0.042 g, 0.000398 mol) was heated in a mixture of ethylene glycol dimethyl ether (4 mL) and water (2 mL) at 80° C for 16 hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature and solvents were removed under the reduced pressure. The residue was purified by preparative HPLC (Hypersil C18, 8μm, 25 cm; 10-60% acetonitrile – 0.1M ammonium acetate over 25 min, 21mL/min) to yield *trans*-3-[4-(1*H*-3-indazolylamino)phenyl]-1-[4-(4-methylpiperazino) cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate (0.035 g, 0.000060 mol) as a white solid.
^{1}H NMR (DMSO-d_6, 400MHz) δ 12.09 (s, 1H), 9.14 (s, 1H), 8.21 (s, 1H), 7.99 (d, 1H), 7.83 (d, 2H), 7.55 (d, 2H), 7.37 (m, 2H), 7.06 (t, 1H), 4.64 (m, 1H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.49 (m, 2H);
RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 12.96 min.
MS: MH^+ 523.

Example 839: *Trans-N*3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-6-(trifluoromethyl)benzo[*d*]isoxazol-3-amine acetate

A. *N*1-(4-bromophenyl)-2-fluoro-4-(trifluoromethyl)benzamide

A solution of 2-fluoro-4-(trifluoromethyl)benzoyl chloride (5.05 g, 0.0223 mol) and 4-bromoaniline (3.83 g, 0.0223 mol) in anhydrous dichloromethane (150 mL) was cooled to 0°C and *N,N*-diisopropylethylamine (4.26 mL, 0.0245 mol) was added under nitrogen atmosphere dropwise. The resulting mixture was stirred at ambient temperature for 24 hours, concentrated and the residue was partitioned between ethyl acetate (120 mL) and water (100 mL). The organic phase was washed

with brine, dried with magnesium sulfate and concentrated. The residue was suspended in cold n-heptane (50 mL) and the precipitate was collected by filtration and dried to yield *N*1-(4-bromophenyl)-2-fluoro-4-(trifluoromethyl)benzamide (7.1 g, 0.0196 mol) as a white solid.

^{1}H NMR (DMSO-d_6, 400MHz) δ 10.74 (s, 1H), 7.90 (m, 2H), 7.74 (d, 1H), 7.68 (d, 2H), 7.56 (d, 2H).

B. *N*1-(4-bromophenyl)-2-fluoro-4-(trifluoromethyl)-1-benzenecarbothioamide

A mixture of *N*1-(4-bromophenyl)-2-fluoro-4-(trifluoromethyl)benzamide (7.1 g, 0.0196 mol) and 2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (3.97 g, 0.0098 mol) was heated in toluene at reflux under an atmosphere of nitrogen for 3 hours. The reaction mixture was cooled to ambient temperature, the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica using ethyl acetate/n-heptane (1:8) as mobile phase to yield *N*1-(4-bromophenyl)-2-fluoro-4-(trifluoromethyl)-1-benzenecarbothioamide (6.0 g, 0.0159 mol) as a yellow solid.

^{1}H NMR (DMSO-d_6, 400MHz) δ 12.33 (s, 1H), 7.94 (d, 2H), 7.81 (m, 2H), 7.65 (m, 3H).

TLC (ethyl acetate / heptane 1:4) R_f 0.61

C. *N*1-(4-bromophenyl)-2-fluoro-4-(trifluoromethyl)-1-benzeneamidoxime

A mixture of *N*1-(4-bromophenyl)-2-fluoro-4-(trifluoromethyl)-1-benzenecarbothioamide (2.50 g, 0.00663 mol), hydroxylamine hydrochloride (0.65 g, 0.00928 mol) and sodium bicarbonate (0.78 g, 0.00928 mol) was heated in absolute ethanol (25 mL) at reflux under nitrogen atmosphere for 14 hours. The reaction mixture was cooled to ambient temperature, the solvent was removed under reduced pressure and the residue partitioned between saturated solution of sodium bicarbonate in water (50 mL) and ethyl acetate (50 mL). The organic phase was washed with brine, dried with magnesium sulfate and concentrated. The residue was suspended in cold n-heptane and the precipitate was collected by filtration and dried

to yield *N*1-(4-bromophenyl)-2-fluoro-4-(trifluoromethyl)-1-benzeneamidoxime (2.35 g, 0.00625 mol) as an off-white solid.

TLC (ethyl acetate / heptane 1:4) R_f 0.12

D. *N*-(4-bromophenyl)-*N*-[6-(trifluoromethyl)benzo[*d*]isoxazol-3-yl]amine

To a solution of *N*1-(4-bromophenyl)-2-fluoro-4-(trifluoromethyl)-1-benzeneamidoxime (2.25 g, 0.00598 mol) in *N*-methylpyrrolidinone (30 mL), potassium *tert*-butoxide (0.71 g, 0.00628 mol) was added and the resulting solution was heated at 100°C under an atmosphere of nitrogen for 3 hours. The reaction mixture was cooled to ambient temperature, the solvent was removed under reduced pressure and the residue partitioned between saturated solution of sodium bicarbonate in water (50 mL) and ethyl acetate (50 mL). The organic phase was washed with brine, dried with magnesium sulfate and concentrated. The residue was suspended in cold n-heptane and the precipitate was collected by filtration and dried to yield *N*-(4-bromophenyl)-*N*-[6-(trifluoromethyl)benzo[*d*]isoxazol-3-yl]amine (1.75 g, 0.0049 mol) as an off-white solid.

^{1}H NMR (DMSO-d_6, 400MHz) δ 9.95 (s, 1H), 8.37 (d, 1H), 8.14 (s, 1H), 7.78 (d, 1H), 7.68 (d, 2H), 7.58 (d, 2H).

TLC (ethyl acetate / heptane 1:5) R_f 0.31

E. *N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-*N*-[6-(trifluoromethyl)benzo[*d*]isoxazol-3-yl]amine

A mixture of *N*-(4-bromophenyl)-*N*-[6-(trifluoromethyl)benzo[*d*]isoxazol-3-yl]amine (1.75 g, 0.0049 mol), diboron pinacol ester (1.49 g, 0.0059 mol), [1.1'-bis(diphenylphosphino) ferrocene]-dichloropalladium (II) complex with dichloromethane (1:1) (0.120 g, 0.000147 mol) and potassium acetate (1.44 g, 0.0144 mol) in *N,N*-dimethylformamide (10 mL) was heated at 80° C under an atmosphere of nitrogen for 16 hours. The mixture was allowed to cool to ambient temperature and the solvent was removed under reduced pressure. Dichloromethane (70 mL) was added to the residue and the resulting solid was removed by filtration through a pad of Celite. The filtrate was concentrated to leave a yellow oil that was purified by flash chromatography on silica using ethyl acetate/ n-heptane (1:6) as

mobile phase to yield *N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-*N*-[6-(trifluoromethyl)benzo[*d*]isoxazol-3-yl]amine (0.065 g, 0.000161 mol) as a white solid.

^{1}H NMR (DMSO-d_6, 400MHz) δ 9.97 (s, 1H), 8.39 (d, 1H), 8.14 (s, 1H), 7.77 (d, 1H), 7.71 (s, 4H), 1.29 (s, 12H).

F. *Trans-N*3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-6-(trifluoromethyl)benzo[*d*]isoxazol-3-amine acetate

A mixture of *N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-*N*-[6-(trifluoromethyl)benzo[*d*]isoxazol-3-yl]amine (0.062 g, 0.000153 mol), *trans*-3-iodo-1-[4-(4-methylpiperazino)-cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.065 g, 0.000146 mol), tetrakis-(triphenylphosphine)palladium (0.010 g, 0.0000087 mol) and sodium carbonate (0.039 g, 0.000365 mol) was heated in a mixture of ethylene glycol dimethyl ether (4 mL) and water (2 mL) at 80° C for 16 hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature and solvents were removed under the reduced pressure. The residue was purified by preparative HPLC (Hypersil C18, 8μm, 25 cm; 10-70% acetonitrile – 0.1M ammonium acetate over 30 min, 21mL/min) to yield *trans-N*3-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-6-(trifluoromethyl)benzo[*d*]isoxazol-3-amine acetate (0.026 g, 0.0000398 mol) as a white solid.

^{1}H NMR (DMSO-d_6, 400MHz) δ 10.05 (s, 1H), 8.44 (d, 1H), 8.23 (s, 1H), 8.16 (s, 1H), 7.88 (d, 2H), 7.79 (d, 1H), 7.69 (d, 2H), 4.67 (m, 1H), 2.6-2.2 (br, 9H), 2.13 (s, 3H), 2.05 (m, 6H), 1.91 (s, 3H), 1.46 (m, 2H);

RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 16.18 min.

MS: MH^+ 592.

Example 840: *N*2-[4-(4-amino-1-{1-[(2-methyl-1*H*-4-imidazolyl)methyl]-4-piperidyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide, dimaleate salt

A. *N*2-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide

3-Iodo-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine, HCl salt (6.75 g, 17.73 mmol), *N*2-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-methyl-1*H*-2-indolecarboxamide (7.571 g, 18.63 mmol), palladium tetrakistriphenyphosphine (1.23 g, 1.06 mmol) and sodium carbonate (8.27 g, 78.03 mmol) were mixed with ethylene glycol dimethyl ether (180 mL) and water (90 mL). The reaction mixture was heated at reflux overnight. Organic solvent was removed under reduced pressure and the aqueous suspension was extracted with copious dichloromethane. The combined organic layer was washed with water then brine, dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash column chromatography using dichloromethane/methanol/ammonium hydroxide (90:10:0.5 to 60:40:0.5) as mobile phase to give *N*2-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide (4.38 g). The aqueous suspension was filtered, washed with water and dried to give *N*2-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide (2.77 g). Combined the solids (7.15 g, 81%). ^{1}H NMR (DMSO-d_6) δ 1.85 (m, 2H), 2.08 (m, 2H), 2.64 (m, 2H), 3.10 (m, 2H), 3.96 (s, 3H), 4.04 (s, 3H), 4.77 (m, 1H), 7.13 (m, 1H), 7.33 (m, 4H), 7.58 (d, J=8.45 Hz, 1H), 7.71 (d, J=7.94 Hz, 1H), 8.12 (d, J=8.15 Hz, 1H), 8.25 (s, 1H), 9.44 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, PH 4.5), 0.8 mL/min.): R_T=1.97 min. MH^+= 497.3.

B. *N*2-[4-(4-amino-1-{1-[(2-methyl-1*H*-4-imidazolyl)methyl]-4-piperidyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide

*N*2-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide (250 mg, 0.503 mmol), 2-methyl-1*H*-4-imidazolecarbaldehyde (83 mg, 0.755 mmol), sodium triacetoxyborohydride (159 mg, 0.755 mmol) and glacial acetic acid (30 mg, 0.554 mmol) were mixed in 1,2-dichloroethane (6 mL). The reaction mixture was stirred

at room temperature overnight. Saturated sodium bicarbonate solution was added to adjust the pH to about 8. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash column chromatography using dichloromethane/methanol/ammonium hydroxide (95:5:0.5 to 80:20:05) as mobile phase to give *N*2-[4-(4-amino-1-{1-[(2-methyl-1*H*-4-imidazolyl)methyl]-4-piperidyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide (215 mg, 72%). ^{1}H NMR (DMSO-d_6) δ 1.91 (m, 2H), 2.23 (m, 7H), 3.00(m, 2H), 3.41 (s, 2H), 3.96 (s, 3H), 4.04 (s, 3H), 4.78 (m, 1H), 6.72 (s, 1H), 7.15 (m, 1H), 7.32 (m, 4H), 7.78 (d, J=8.43 Hz, 1H), 7.70 (d, J=7.92 Hz, 1H), 8.11 (d, J=7.92 Hz, 1H), 8.24 (s, 1H), 9.44 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, PH 4.5), 0.8 mL/min.): R_T=2.00 min. MH^+= 591.3.

C. *N*2-[4-(4-amino-1-{1-[(2-methyl-1*H*-4-imidazolyl)methyl]-4-piperidyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide, dimaleate salt

*N*2-[4-(4-amino-1-{1-[(2-methyl-1*H*-4-imidazolyl)methyl]-4-piperidyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide (210 mg, 0.355 mmol) was dissolved in hot ethyl acetate (25 mL) and a few drops of ethanol. Maleic acid (83mg, 0.711 mmol) in hot ethyl acetate (3 mL) was added. The reaction mixture was stirred at room temperature for 3 hours. The solid was collected by filtration to give *N*2-[4-(4-amino-1-{1-[(2-methyl-1*H*-4-imidazolyl)methyl]-4-piperidyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide, dimaleate salt (255 mg, 87%). ^{1}H NMR (DMSO-d_6) δ 2.12 (m, 2H), 2.43 (m, 5H), 2.92 (m, 2H), 3.38 (m, 2H), 3.96 (s, 3H), 3.99 (s, 2H), 4.04 (s, 3H), 4.93 (m, 1H), 6.13 (s, 4H), 7.16 (m, 1H), 7.34 (m, 5H), 7.60 (d, J=8.43 Hz, 1H), 7.70 (d, J=7.92 Hz, 1H), 7.72 (d, J=8.15 Hz, 1H), 8.27 (s, 1H), 9.44 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC-Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5

min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, PH 4.5), 0.8 mL/min.): R_T=1.98 min. MH^+= 591.3.

Example 841: *N*2-(4-{4-amino-1-[1-(1*H*-4-imidazolylmethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide, dimaleate salt

A. *N*2-(4-{4-amino-1-[1-(1*H*-4-imidazolylmethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide, diacetate salt

*N*2-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide (250 mg, 0.503 mmol), 1*H*-4-imidazolecarbaldehyde (73 mg, 0.755 mmol), sodium triacetoxyborohydride (159 mg, 0.755 mmol) and glacial acetic acid (30 mg, 0.554 mmol) were mixed in 1,2-dichloroethane (6 mL). The reaction mixture was stirred at room temperature overnight. Saturated sodium bicarbonate solution was added to adjust the pH to about 8. The layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated. The residue was first purified by flash column chromatography using dichloromethane/methanol/ammonium hydroxide (95:5:0.5 to 80:20:05) as mobile phase then purified again by reverse phase preparative HPLC using acetonitrile/water (50mM ammonium acetate buffer) as mobile phase to give *N*2-(4-{4-amino-1-[1-(1*H*-4-imidazolylmethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide, diacetate salt (170 mg, 49%). ^{1}H NMR (DMSO-d_6) δ 1.90 (m, 8H), 2.20 (m, 4H), 2.99 (m, 2H), 3.47(s, 2H), 3.96 (s, 3H), 4.04 (s, 3H), 4.67 (m, 1H), 7.15 (m, 1H), 7.31 (m, 5H), 7.54 (s, 1H), 7.58 (d, J=8.43 Hz, 1H), 7.70 (d, J=7.95 Hz, 1H), 8.10 (d, J=8.14 Hz, 1H), 8.24 (s, 1H), 9.44 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, PH 4.5), 0.8 mL/min.): R_T=1.97 min. MH^+= 577.3.

B. *N*2-(4-{4-amino-1-[1-(1*H*-4-imidazolylmethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-

indolecarboxamide, dimaleate salt

*N*2-(4-{4-amino-1-[1-(1*H*-4-imidazolylmethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide, diacetate salt (170 mg, 0.244 mmol) was dissolved in hot ethyl acetate (25 mL) and a few drops of ethanol. Maleic acid (103mg, 0.884 mmol) in hot ethyl acetate (3 mL) was added. The reaction mixture was stirred at room temperature for 3 hours. The solid was collected by filtration to give *N*2-(4-{4-amino-1-[1-(1*H*-4-imidazolylmethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide, dimaleate salt (153 mg, 76%). ^{1}H NMR (DMSO-d_6) δ 2.19 (m, 2H), 2.49 (m, 2H), 3.19 (m, 2H), 3.52 (m, 2H), 3.96 (s, 3H), 4.04 (s, 3H), 4.21 (s, 2H), 5.02 (m, 1H), 6.15 (s, 4H), 7.16 (m, 1H), 7.32 (m, 5H), 7.40 (s, 1H), 7.59 (d, J=8.45 Hz, 1H), 7.71 (d, J=7.95 Hz, 1H), 7.98 (bs, 1H), 8.13 (d, J=8.16 Hz, 1H), 8.27 (s, 1H), 9.44 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, PH 4.5), 0.8 mL/min.): R_T=1.98 min. MH^+= 577.3.

Example 842: *N*2-(4-{4-amino-1-[1-(2-fluoroethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide, dimaleate salt

A. *N*2-(4-{4-amino-1-[1-(2-fluoroethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide

*N*2-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide (250 mg, 0.503 mmol), 1-bromo-2-fluoroethane (47 ul, 0.629 mmol), Potassium carbonate (87 mg, 0.629 mmol) and Sodium iodide (10 mg, 0.066 mmol) were mixed in DMF (3 mL). The reaction mixture was heated at 80°C overnight. The crude reaction mixture was purified by reverse phase preparative HPLC using acetonitrile/water (50mM ammonium acetate buffer) as mobile phase to give *N*2-(4-{4-amino-1-[1-(2-fluoroethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide (221 mg, 81%). ^{1}H NMR (DMSO-d_6) δ 1.91 (m,

2H), 2.26 (m, 4H), 2.66 (m, 1H), 2.73 (m, 1H), 3.05 (m, 2H), 3.97 (s, 3H), 4.04 (s, 3H), 4.61 (m, 1H), 4.61 (m, 1H), 4.64 (m, 1H), 7.15 (m, 1H), 7.33 (m, 4H), 7.58 (d, J=8.46 Hz, 1H), 7.70 (d, J=7.95 Hz, 1H), 8.11 (d, J=8.14 Hz, 1H), 8.25 (s, 1H), 9.44 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, PH 4.5), 0.8 mL/min.): R_T=2.17 min. MH^+= 543.3.

B. *N*2-(4-{4-amino-1-[1-(2-fluoroethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide, dimaleate salt

*N*2-(4-{4-amino-1-[1-(2-fluoroethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide (221 mg, 0.407 mmol) was dissolved in hot ethyl acetate (25 mL) and a few drops of ethanol. Maleic acid (94mg, 0.814 mmol) in hot ethyl acetate (3 mL) was added. The reaction mixture was stirred at room temperature overnight. No precipitate was formed. The organic solvent was removed and the solid was triturated with ethyl acetate. The solid was collected by filtration to give *N*2-(4-{4-amino-1-[1-(2-fluoroethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide, dimaleate salt (252 mg, 80%). ^{1}H NMR (DMSO-d_6) δ 2.34 (m, 2H), 2.54 (m, 2H), 3.49-3.67(m, 6H), 3.96 (s, 3H), 4.04 (s, 3H), 4.81 (m, 1H), 4.92 (m, 1H), 5.06 (m, 1H), 6.14 (s, 4H), 7.16 (m, 1H), 7.34 (m, 4H), 7.60 (d, J=8.32 Hz, 1H), 7.70 (d, J=7.95 Hz, 1H), 8.14 (d, J=8.15 Hz, 1H), 8.29 (s, 1H), 9.45 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, PH 4.5), 0.8 mL/min.): R_T=2.17 min. MH^+= 543.3.

Example 843: *N*2-(4-{4-amino-1-[1-(2,2-difluoroethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide, dimaleate salt

A. *N*2-(4-{4-amino-1-[1-(2,2-difluoroethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-

indolecarboxamide

*N*2-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide (250 mg, 0.503 mmol), 2-bromo-1,1-difluoroethane (91 mg, 0.629 mmol), Potassium carbonate (87 mg, 0.629 mmol) and Sodium iodide (10 mg, 0.066 mmol) were mixed in DMF (3 mL). The reaction mixture was heated at 80°C overnight. HPLC showed only about fifty percent conversion. The bath temperature was lowered to 55°C and more 2-bromo-1,1-difluoroethane (0.1 mL) was added. After stirring at 55°C overnight, more 2-bromo-1,1-difluoroethane (0.1 mL) was added and the reaction mixture was stirred at 55°C overnight. HPLC showed most of starting material was converted to product. The crude reaction mixture was purified by reverse phase preparative HPLC using acetonitrile/water (50mM ammonium acetate buffer) as mobile phase to give *N*2-(4-{4-amino-1-[1-(2,2-difluoroethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide (227 mg, 81%). ^{1}H NMR (DMSO-d_6) δ 1.89 (m, 2H), 2.27 (m, 2H), 2.42 (m, 2H), 2.80 (m, 1H), 3.05 (m, 2H), 3.96 (s, 3H), 4.04 (s, 3H), 4.69 (m, 1H), 6.17 (t t, J=55.81 Hz, J=4.35 Hz, 1H), 7.15 (m, 1H), 7.33 (m, 4H), 7.78 (d, J=7.94 Hz, 1H), 7.70 (d, J=7.94 Hz, 1H), 8.11 (d, J=8.19 Hz, 1H), 8.25 (s, 1H), 9.44 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, PH 4.5), 0.8 mL/min.): R_T=3.32 min. MH^+= 561.3.

B. *N*2-(4-{4-amino-1-[1-(2,2-difluoroethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide, dimaleate salt

*N*2-(4-{4-amino-1-[1-(2,2-difluoroethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide (227 mg, 0.405 mmol) was dissolved in hot ethyl acetate (25 mL). Maleic acid (94 mg, 0.810 mmol) in hot ethyl acetate (3 mL) was added. The reaction mixture was stirred at room temperature overnight. No precipitate was formed. After stirring at room temperature for 4 days, precipitate was formed at bottom of the flask. The solvent was decanted. The solid was washed with ethyl acetate and dried to give *N*2-(4-{4-amino-1-[1-(2,2-difluoroethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-

methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide, dimaleate salt (220 mg, 68 %). ^{1}H NMR (DMSO-d_6) δ 2.05 (m, 2H), 2.40 (m, 2H), 2.84-3.32 (bm, 6H), 3.96 (s, 3H), 4.04 (s, 3H), 4.85 (m, 1H), 6.22 (s, 4H), 6.34 (t, J=56.07 Hz, 1H), 7.15 (m, 1H), 7.33 (m, 4H), 7.59 (d, J=8.45 Hz, 1H), 7.70 (d, J=7.94 Hz, 1H), 8.12 (d, J=8.19 Hz, 1H), 8.28 (s, 1H), 9.45 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, PH 4.5), 0.8 mL/min.): R_T=3.32 min. MH^+= 561.3.

Example 844: *N*2-{4-[4-amino-1-(1-ethyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide

*N*2-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide (250 mg, 0.503 mmol), acetaldehyde (44 mg, 1.007 mmol) and sodium triacetoxyborohydride (212 mg, 1.007 mmol) were mixed in 1,2-dichloroethane (6 mL). The reaction mixture was stirred at room temperature overnight. The solvent was removed and the residue was purified by reverse phase preparative HPLC using acetonitrile/water (50mM ammonium acetate buffer) as mobile phase to give *N*2-{4-[4-amino-1-(1-ethyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide (247 mg, 93%). ^{1}H NMR (DMSO-d_6) δ 1.04 ((t, J=7.15 Hz, 3H), 1.92 (m, 2H), 2.08 (m, 2H), 2.25 (m, 2H), 2.40 (q, J=7.15 Hz, 2H), 3.03 (m, 2H), 3.96 (s, 3H), 4.04 (s, 3H), 4.68 (m, 1H), 7.13 (m, 1H), 7.33 (m, 4H), 7.58 (d, J=8.00Hz, 1H), 7.70 (d, J=7.95 Hz, 1H), 8.11 (d, J=8.15 Hz, 1H), 8.25 (s, 1H), 9.44 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, PH 4.5), 0.8 mL/min.): R_T=2.08 min. MH^+= 525.3.

Examples 845- were made using the methods described in Example 844.

Example 845: *N*2-[4-(4-amino-1-{1-[(3-methyl-1*H*-4-pyrazolyl)methyl]-4-

piperidyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide, Acetate salt

Yield: 187 mg, 63%

^{1}H NMR (DMSO-d_6) δ 1.91 (m, 2H), 2.09 (m, 2H), 2.19 (m, 5H), 2.96 (m, 2H), 3.35 (s, 2H), 3.96 (s, 3H), 4.04 (s, 3H), 4.67 (m, 1H), 7.17 (m, 1H), 7.31 (m, 5H), 7.58 (d, J=8.46 Hz, 1H), 7.70 (d, J=7.94 Hz, 1H), 8.10 (d, J=8.15 Hz, 1H), 8.24 (s, 1H), 9.44 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, PH 4.5), 0.8 mL/min.): R_T=2.03 min. MH^+= 591.3.

Example 846: *N*2-(4-{4-amino-1-[1-(3-furylmethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide Yield 233 mg, 80%

^{1}H NMR (DMSO-d_6) δ 1.91 (m, 2H), 2.13-2.23 (m, 4H), 3.00 (m, 2H), 3.39 (s, 2H), 3.96 (s, 3H), 4.04 (s, 3H), 4.68 (m, 1H), 6.47 (s, 1H), 7.31 (m, 4H), 7.60 (m, 3H), 7.70 (d, J=7.94 Hz, 1H), 8.11 (d, J=8.05 Hz, 1H), 8.24 (s, 1H), 9.44 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, PH 4.5), 0.8 mL/min.): R_T=2.37 min. MH^+= 577.3.

Example 847: *N*2-{4-[4-amino-1-(1-tetrahydro-2*H*-4-pyranyl-4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide

The reaction was carried out at 70°C overnight instead of room temperature overnight as described in the example 844.

Yield 176 mg, 71%.

^{1}H NMR (DMSO-d_6) δ 1.46(m, 2H), 1.71 (m, 2H), 1.91 (m, 2H), 2.20 (m, 2H), 2.30 (m, 2H), 3.07 (m, 3H), 3.27 (m, 2H), 3.91(m, 2H), 3.96 (s, 3H), 4.04 (s, 3H), 4.67 (m, 1H), 7.15 (m, 1H), 7.33 (m, 4H), 7.58 (d, J=8.44 Hz, 1H), 7.70 (d, J=7.94 Hz, 1H), 8.10 (d, J=8.04 Hz, 1H), 8.24 (s, 1H), 9.44 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 um, 33x4.6 mm.

Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, PH 4.5), 0.8 mL/min.): R_T=2.08 min. MH^+= 581.3.

Example 848: *N*2-(4-{4-amino-1-[(1-acetylpiperidin-4-yl)- piperidin-4-yl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide

The reaction was carried out at 70°C overnight instead of room temperature overnight as described in the Example 844.

Yield 223 mg, 71%.

^{1}H NMR (DMSO-d_6) δ 1.28 (m, 1H), 1.43 (m, 1H), 1.75 (m, 2H), 1.91 (m, 2H), 1.99 (s, 3H), 2.19 (m, 2H), 2.34 (m, 2H), 2.54 (m, 2H), 3.01 (m, 3H), 3.83 (m, 1H), 3.96 (s, 3H), 4.04 (s, 3H), 4.38 (m, 1H), 4.66 (m, 1H), 7.15 (m, 1H), 7.31 (m, 4H), 7.78 (d, J=7.94 Hz, 1H), 7.70 (d, J=7.94 Hz, 1H), 8.11 (d, J=8.15 Hz, 1H), 8.24 (s, 1H), 9.44 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, PH 4.5), 0.8 mL/min.): R_T=1.97 min. MH^+= 622.3.

Example 849: *N*2-(4-{4-amino-1-[1-(4-pyridylmethyl)-4-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide

Yield 57 mg, 18%.

^{1}H NMR (DMSO-d_6) δ 1.91 (m, 2H), 2.28 (m, 4H), 3.95 (m, 2H), 3.59 (s, 2H), 3.96 (s, 3H), 4.04 (s, 3H), 4.71 (m, 1H), 7.17 (m, 1H), 7.34 (m, 6H), 7.59 (d, J=8.03Hz, 1H), 7.71 (d, J=7.94 Hz, 1H), 8.11 (d, J=8.14 Hz, 1H), 8.25 (s, 1H), 8.52 (d, J=5.78 Hz, 2H), 9.44 (s, 1H). LCMS (Thermoquest AQA single Quad MS, Finnigan HPLC- Column: Genesis, C18, 3 um, 33x4.6 mm. Eluents: 30% B/A to 95% B/A in 4.5 min. (B: acetonitrile, A: 50 mM ammonia acetate buffer, PH 4.5), 0.8 mL/min.): R_T=2.50 min. MH^+= 588.3.

Example 850: N2-(4-{4-amino-1-[3-(4-methylpiperazino)propyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1H-2-indolecarboxamide

A. 1-(3-bromopropyl)-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

A suspension of 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (10.00 g, 38.31 mmol) in tetrahydrofuran (150 mL) was treated with 3-bromo-1-propanol (15.98 g, 114.93 mmol) and triphenylphosphine (20.1 g, 76.62 mmol). Diethylazodicarboxyate (13.34 g, 76.62 mmol) was slowly added to the reaction mixture. The reaction mixture was stirred at 0°C for 30 min, after which the ice bath was removed and was stirred for 30 minutes at room temperature. The reaction mixture was partially concentrated and ethyl acetate (200 mL) was added. The precipitate was filtered and the filtrate was concentrated to dryness. The crude compound was purified by flash chromatography on silica gel using 100% ethyl acetate as the eluent. The afforded 7.8 g (53%) of 1-(3-bromopropyl)-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.230 (s, 1H), 4.419-4.385 (t, 2H), 3.530-3.498 (t, 2H), 2.370-2.304 (q, 2H); LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3μm particle size, 33 x 4.6mm; 70 % 50 mM ammonium acetate in water to 95% acetonitrile over 6 min, 0.8 to 0.5 mL/min) R_t 2.05 min (100%), MH^+ 422.9.

B. 3-iodo-1-[3-(4-methylpiperazino)propyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

A suspension of 1-(3-bromopropyl)-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.500 g, 1.31 mmol) in dimethylformamide (10 mL) was treated with 1-methylpiperazine (0.157 g, 1.572 mmol) and triethylamine (0.133 g, 1.31 mmol). The reaction mixture was stirred at 70°C for 66.25 h. Solvent was removed under reduced pressure. Dichloromethane (15 mL) and 1 N hydrochloric acid (20 mL) were added. The layers were partitioned and the aqueous layer was washed with dichloromethane (100 mL). The aqueous layer was neutralized to pH 13 and then extracted with dichloromethane (250 mL). The organic layer was dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude material was purified by flash chromatography on silica gel using a step-wise gradient; 20% methanol in dichloromethane to 50% methanol in dichloromethane

over 55 minutes on a 35 g ISCO column. The column afforded 0.238 g (45%) of pure 3-iodo-1-[3-(4-methylpiperazino)propyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.191 (s, 1H), 4.308-4.273 (t, 2H), 2.262-2.228 (m, 10H), 1.944-1.877(m, 2H); LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3μm particle size, 33 x 4.6mm; 70 % 50 mM ammonium acetate in water to 95% acetonitrile over 6 min, 0.8 to 0.5 mL/min) R_t 0.75 min (100%), MH^+ 402.1.

C. *N*2-(4-{4-amino-1-[3-(4-methylpiperazino)propyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide

A solution of 3-iodo-1-[3-(4-methylpiperazino)propyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.188 g, 0.469 mmol) in ethylene glycol dimethyl ether (16 mL) was treated with *N*2-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-methyl-1*H*-2-indolecarboxamide (0.209 g, 0.516 mmol), tetrakis(triphenylphosphine)palladium (0.033 g, 0.028 mmol), and a solution of sodium carbonate (0.119 g, 1.13 mmol) in water (8 mL). The reaction mixture was stirred for 4.5 h at 80°C. The organic solvent was removed under reduced pressure and ethyl acetate (200 mL) was added. The layers were partitioned and the aqueous layer was extracted with ethyl acetate (400 mL). The combined organic layers were dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude material was purified by flash chromatography on silica gel using a step-wise gradient of 20% methanol in dichloromethane to 50% methanol in dichloromethane. The column afforded 0.078 g (30%) of pure *N*2-(4-{4-amino-1-[3-(4-methylpiperazino)propyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.442 (s, 1H), 8.258 (s, 1H), 8.122-8.1076 (d, 1H, J = 8.16 Hz), 7.719-7.6991 (d, 1H, J = 7.96 Hz), 7.6005-7.5793 (d, 1H, J = 8.48 Hz), 7.349-7.294 (m, 4H), 7.172-7.135 (t, 1H), 4.405-4.371 (m, 2H), 4.04 (s, 3H), 3.958 (s, 3H), 3.291 (m, 2H), 2.5 (m, 3H), 2.45-2.337 (m, 5H), 2.30-2.10 (m, 3H), 2.022-2.005 (m, 2H); LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3μm particle size, 33 x 4.6mm; 70 % 50 mM ammonium acetate in water to 95% acetonitrile over 6 min, 0.8 to 0.5 mL/min) R_t 2.05 min (100%), MH^+ 554.3.

Example 851: *N*2-{4-[4-amino-1-(3-morpholinopropyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide

A. 3-iodo-1-(3-morpholinopropyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

A suspension of 1-(3-bromopropyl)-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-

amine (0.500 g, 1.31 mmol) in dimethylformamide (10 mL) was treated with morpholine (0.137 g, 1.572 mmol) and triethylamine (0.133 g, 1.31 mmol). The reaction mixture was stirred at 70°C for 66.25 h. Solvent was removed under reduced pressure. Dichloromethane (15 mL) and 1 N hydrochloric acid (20 mL) were added. The layers were partitioned and the aqueous layer was washed with dichloromethane (100 mL). The aqueous layer was neutralized to pH 14 and then extracted with dichloromethane (250 mL). The organic layer was dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude material was purified by flash chromatography on silica gel using a step-wise gradient of 10% methanol in dichloromethane to 50% methanol in dichloromethane over 58 minutes on a 35 g ISCO column. The column afforded 0.244 g (48%) of pure 3-iodo-1-(3-morpholinopropyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.194 (s, 1H), 4.327-4.293 (t, 2H), 3.485-3.364 (m, 4H), 2.253-2.238 (m, 6H), 1.963-1.895(m, 2H); LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3μm particle size, 33 x 4.6mm; 70 % 50 mM ammonium acetate in water to 95% acetonitrile over 6 min, 0.8 to 0.5 mL/min) R_t 0.71 min (100%), MH^+ 389.0.

B. *N*2-{4-[4-amino-1-(3-morpholinopropyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide

A solution of 3-iodo-1-(3-morpholinopropyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.244 g, 0.629 mmol) in ethylene glycol dimethyl ether (16 mL) was treated with *N*2-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-methyl-1*H*-2-indolecarboxamide (0.281 g, 0.692 mmol), tetrakis(triphenylphosphine)palladium (0.044 g, 0.038 mmol), and a solution of sodium carbonate (0.160 g, 1.51 mmol) in water (8 mL). The reaction mixture was stirred for 4.5 h at 80°C. The organic solvent was removed under reduced pressure and ethyl acetate (200 mL) was added. The layers were partitioned and the aqueous layer was extracted with ethyl acetate (400 mL). The combined organic layers were dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude material was purified by flash chromatography on silica gel using a step-wise gradient of 10% methanol in dichloromethane to 50% methanol in dichloromethane

as the eluent. The column afforded 0.191 g (56%) of pure *N*2-{4-[4-amino-1-(3-morpholinopropyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.440 (s, 1H), 8.260 (s, 1H), 8.1229-8.1026 (d, 1H, *J* = 8.12 Hz), 7.7184-7.6986 (d, 1H, *J* = 7.92 Hz), 7.5983-7.578 (d, 1H, *J* = 8.08 Hz), 7.345-7.290 (m, 4H), 7.172-7.133 (m, 1H), 4.421-4386 (m, 2H), 4.04 (s, 3H), 3.958 (s, 3H), 3.521-3.500 (m, 4H), 2.349-2.314 (m, 6H), 2.035-2.001 (m, 2H); LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3μm particle size, 33 x 4.6mm; 70 % 50 mM ammonium acetate in water to 95% acetonitrile over 6 min, 0.8 to 0.5 mL/min) R_t 2.05 min (100%), MH^+ 541.3.

Example 852: *N*2-(4-{4-amino-1-[3-(1*H*-1-imidazolyl)propyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide

A. 1-[3-(1*H*-1-imidazolyl)propyl]-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

A suspension of 1-(3-bromopropyl)-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.500 g, 1.31 mmol) in dimethylformamide (10 mL) was treated with imidazole (0.107 g, 1.572 mmol) and triethylamine (0.133 g, 1.31 mmol). The reaction mixture was stirred at 70°C for 25.5 h. Solvent was removed under reduced pressure. Dichloromethane (15 mL) and 1 N hydrochloric acid (20 mL) were added. The layers were partitioned and the aqueous layer was washed with dichloromethane (100 mL). The aqueous layer was neutralized to pH 14 and then extracted with dichloromethane (250 mL). The organic layer was dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude material was purified by flash chromatography on silica gel using 10% methanol in dichloromethane as the eluent. The column afforded 0.086 g (18%) of pure 1-[3-(1*H*-1-imidazolyl)propyl]-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.211 (s, 1H), 7.896 (s, 1H), 7.264 (s, 1H), 6.96 (s, 1H), 4.32-4.227 (m, 2H), 4.011-3.977 (m, 2H), 2.329-2.215 (m, 2H); LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3μm particle size, 33 x 4.6mm; 70 % 50 mM ammonium acetate in water to 95% acetonitrile over 6 min,

0.8 to 0.5 mL/min) R_t 0.46 min (100%), MH^+ 370.0.

B. *N*2-(4-{4-amino-1-[3-(1*H*-1-imidazolyl)propyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide

A suspension of 1-[3-(1*H*-1-imidazolyl)propyl]-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.086 g, 0.233 mmol) in ethylene glycol dimethyl ether (4 mL) was treated with *N*2-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-methyl-1*H*-2-indolecarboxamide (0.104 g, 0.256 mmol), tetrakis(triphenylphosphine)palladium (0.016 g, 0.014 mmol), and a solution of sodium carbonate (0.059 g, 0.56 mmol) in water (2 mL). The reaction mixture was stirred for 24 h at 80°C. The organic solvent was removed under reduced pressure and dichloromethane (25 mL) was added. The layers were partitioned and the aqueous layer was extracted with dichloromethane (100 mL). The combined organic layers were dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude material was purified by flash chromatography on silica gel using a step-wise gradient of 5% methanol in dichloromethane to 50% methanol in dichloromethane on a 10 g ISCO column. The column afforded 0.06 g (49%) of pure *N*2-(4-{4-amino-1-[3-(1*H*-1-imidazolyl)propyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.443 (s, 1H), 8.278 (s, 1H), 8.1324-8.1121 (d, 1H, J = 8.12 Hz), 7.744-7.699 (m, 2H), 7.6-7.579 (d, 1H, J = 8.4 Hz), 7.365-7.283 (m, 5H), 7.172-7.135 (m, 1H), 6.939 (s, 1H), 4.36-4.326 (m, 2H), 4.079-4.019 (m, 5H), 3.964 (s, 3H), 2.324-2.309 (m, 2H); LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3μm particle size, 33 x 4.6mm; 70 % 50 mM ammonium acetate in water to 95% acetonitrile over 6 min, 0.8 to 0.5 mL/min) R_t 2.25 min (100%), MH^+ 522.3.

Example 853: *N*2-[4-(4-amino-1-tetrahydro-1*H*-3-pyrrolyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide

A. *tert*-butyl 3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-pyrrolidinecarboxylate

A suspension of 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (5.0 g, 19.15

mmol) in tetrahydrofuran (100 mL) was treated with tert-butyl 3-hydroxy-1-pyrrolidinecarboxylate (5.38 g, 28.73 mmol) and triphenylphosphine (7.53 g, 28.73 mmol). The reaction mixture was cooled to 0°C on an ice bath. Diethylazodicarboxyate (5.0 g, 28.73 mmol) was slowly added to the reaction mixture. The solvent was removed under reduced pressure after 6 days. The crude oil was used directly in the subsequent reaction without further analysis.

B. 3-iodo-1-tetrahydro-1*H*-3-pyrrolyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine hydrochloride

A suspension of the crude tert-butyl 3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-pyrrolidinecarboxylate in acetone (100 mL) was treated with 6 N hydrochloric acid (50 mL). The reaction mixture was stirred at 40°C for 15 hours. The initial precipitate was filtered and confirmed by LCMS to be impurities. The reaction mixture was allowed to sit at room temperature and a precipitate formed over night. The precipitate was filtered and washed with diethyl ether. The filtration afforded 2.186 g (31%) of pure 3-iodo-1-tetrahydro-1*H*-3-pyrrolyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine hydrochloride. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.8815 (s, 1H), 8.9923 (br.s, 1H), 8.4803 (s, 1H), 7.82 (br.s, 1H), 5.5908-5.5295 (m, 1H), 3.7131-3.6706 (m, 1H), 3.5590-3.5003 (m, 1H), 3.4466-3.4174 (m, 2H), 2.4592-2.4255 (m, 1H), 2.4064-2.3146 (m, 1H); LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3μm particle size, 33 x 4.6mm; 70 % 50 mM ammonium acetate in water to 95% acetonitrile over 6 min, 0.8 to 0.5 mL/min) R_t 1.09 min (100%), MH^+ 331.0.

C. *N*2-[4-(4-amino-1-tetrahydro-1*H*-3-pyrrolyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide

A suspension of 3-iodo-1-tetrahydro-1*H*-3-pyrrolyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine hydrochloride (2.186 g, 5.96 mmol) in ethylene glycol dimethyl ether (50 mL) was treated with *N*2-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-methyl-1*H*-2-indolecarboxamide (2.66 g, 6.56 mmol), tetrakis(triphenylphosphine)palladium (0.413g, 0.358 mmol), and a solution of sodium carbonate (2.65 g, 25.03 mmol) in water (25 mL). The reaction mixture

was stirred for 24 h at 80°C. The organic solvent was removed under reduced pressure. Dichloromethane (100 mL) and 1N sodium hydroxide (50 mL) were added. The product precipitated out of the aqueous layer. The aqueous layer was evaporated under reduced pressure. The resulting solid was washed with copious amounts of dichloromethane and ethyl acetate. The organic solvent was removed under reduced pressure to give 2.218 g (77%) of pure *N*2-[4-(4-amino-1-tetrahydro-1*H*-3-pyrrolyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.443 (s, 1H), 8.256 (s, 1H), 8.1168-8.0965 (d, 1H, *J* = 8.12 Hz), 7.7181-7.6983 (d, 1H, *J* = 7.92 Hz), 7.598-7.5778 (d, 1H, *J* = 8.08 Hz), 7.349-7.291 (m, 4H), 7.171-7.132 (m, 1H), 5.332-5.313 (m, 1H), 4.041 (s, 3H), 3.96 (s, 3H), 3.224-3.058 (m, 3H), 2.926-2.910 (m, 1H), 2.213-2.158 (m, 2H); LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3μm particle size, 33 x 4.6mm; 70 % 50 mM ammonium acetate in water to 95% acetonitrile over 6 min, 0.8 to 0.5 mL/min) R_t 2.09 min (100%), MH^+ 483.3.

Example 854: *N*2-[4-(4-amino-1-{1-[(1-methyl-1*H*-2-imidazolyl)methyl]tetrahydro-1*H*-3-pyrrolyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide

A suspension of *N*2-[4-(4-amino-1-tetrahydro-1*H*-3-pyrrolyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide (0.250 g, 0.518 mmol) in dichloroethane (5 mL) was treated with 1-methyl-2-imidazolecarboxaldehyde (0.115 g, 1.04 mmol) and sodium triacetoxy borohydride (0.220 g, 1.04 mmol). The reaction mixture was stirred at room temperature for 18 h under a nitrogen atmosphere. Sodium hydroxide (1N, 15 mL) was added to the reaction mixture and was stirred for 1h. The organic layer was removed under reduced pressure and dichloromethane was added. The layers were partitioned and the aqueous layer was extracted with dichloromethane (200 mL). The combined organic layers were dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude material was purified by flash chromatography on silica gel using 10% methanol in dichloromethane (15 min), 15% methanol in dichloromethane (15 min), 20% methanol in dichloromethane (20 min) and 50% methanol in dichloromethane (5 min) as the eluent. The column

afforded 0.060 g (20%) of pure *N*2-[4-(4-amino-1-{1-[(1-methyl-1*H*-2-imidazolyl)methyl]tetrahydro-1*H*-3-pyrrolyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide. ^{1}H NMR (DMSO-d_6, 400 MHz) δ□9.446 (s, 1H), 8.249 (s, 1H), 8.1312-8.1108 (d, 1H, *J* = 8.16 Hz), 7.7207-7.7008 (d, 1H, *J* = 7.96 Hz), 7.6023-7.5812 (d, 1H, *J* = 8.44 Hz), 7.356-7.293 (m, 4H), 7.174-7.120 (m, 2H), 6.822 (s, 1H), 5.425-5.391 (m, 1H), 4.044 (s, 3H), 3.962 (s, 3H), 3.693 (m, 2H), 3.651 (s, 3H), 2.86-2.797 (m, 3H), 2.368-2.323 (m, 2H); LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3μm particle size, 33 x 4.6mm; 70 % 50 mM ammonium acetate in water to 95% acetonitrile over 6 min, 0.8 to 0.5 mL/min) R_t 2.34 min (100%), MH^+ 577.3.

Example 855: *N*2-{4-[4-amino-1-(1-isopropyltetrahydro-1*H*-3-pyrrolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide

A suspension of *N*2-[4-(4-amino-1-tetrahydro-1*H*-3-pyrrolyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide (0.250 g, 0.518 mmol) in dichloroethane (5 mL) was treated with acetone (1.96 g, 33.15 mmol) and sodium triacetoxy borohydride (0.220 g, 1.04 mmol). The reaction mixture was stirred at room temperature for 18 h under a nitrogen atmosphere. Sodium hydroxide (1N, 15 mL) was added to the reaction mixture and was stirred for 1h. The organic layer was removed under reduced pressure and dichloromethane was added. The layers were partitioned and the aqueous layer was extracted with dichloromethane (200 mL). The combined organic layers were dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude material was purified by flash chromatography on silica gel using 10% methanol in dichloromethane (15 min), 15% methanol in dichloromethane (15 min), 20% methanol in dichloromethane (20 min) and 50% methanol in dichloromethane (5 min) as the eluent. The column afforded 0.123 g (44%) of pure *N*2-{4-[4-amino-1-(1-isopropyltetrahydro-1*H*-3-pyrrolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.449 (s, 1H), 8.265 (s, 1H), 8.127-8.1068 (d, 1H, *J* = 8.08 Hz), 7.7196-7.6999 (d, 1H, *J* = 7.88 Hz), 7.6013-7.5803 (d, 1H, *J* = 8.4 Hz), 7.351-7.299 (m, 4H), 7.173-7.135 (m, 1H), 5.394 (m,

1H), 4.042 (s, 3H), 3.961 (s, 3H), 2.793 (m, 3H), 2.337 (m, 3H), 1.068 (br.s, 6H); LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3μm particle size, 33 x 4.6mm; 70 % 50 mM ammonium acetate in water to 95% acetonitrile over 6 min, 0.8 to 0.5 mL/min) R_t 2.38 min (100%), MH^+ 525.3.

Example 856: *N*2-(4-{4-amino-1-[1-(2-methoxyethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide

A suspension of *N*2-[4-(4-amino-1-tetrahydro-1*H*-3-pyrrolyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide (0.250 g, 0.518 mmol) in dimethylformamide (5 mL) was treated with 2-bromoethyl methyl ether (0.079 g, 0.569 mmol) and potassium carbonate (0.143g, 1.04 mmol). The reaction mixture was stirred at 65°C for 18 h under a nitrogen atmosphere. Water (25 mL) was added to the reaction mixture. The precipitate formed was filtered and dried on the lyophilizer. The crude material was purified by flash chromatography on silica gel using 10% methanol in dichloromethane (15 min), 15% methanol in dichloromethane (15 min), 20% methanol in dichloromethane (20 min) and 50% methanol in dichloromethane (5 min) as the eluent. The column afforded 0.082 g (29%) of pure *N*2-(4-{4-amino-1-[1-(2-methoxyethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.447 (s, 1H), 8.265 (s, 1H), 8.1278-8.1075 (d, 1H, J = 8.12 Hz), 7.7192-7.6993 (d, 1H, J = 7.96 Hz), 7.5996-7.5799 (d, 1H, J = 7.88 Hz), 7.349-7.295 (m, 4H), 7.172-7.133 (m, 1H), 5.42 (m, 1H), 4.042 (s, 3H), 3.96 (s, 3H), 3.479 (m, 2H), 3.266-3.258 (m, 3H), 2.95-2.60 (m, 4H), 2.332 (m, 2H); LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3μm particle size, 33 x 4.6mm; 70 % 50 mM ammonium acetate in water to 95% acetonitrile over 6 min, 0.8 to 0.5 mL/min) R_t 2.34 min (100%), MH^+ 541.3.

Example 857: *N*2-(4-{4-amino-1-[1-(1*H*-4-imidazolylmethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide

A suspension of *N*2-[4-(4-amino-1-tetrahydro-1*H*-3-pyrrolyl-1*H*-

pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide (0.200 g, 0.415 mmol) in dichloroethane (5 mL) was treated with 4-formylimidazole (0.08 g, 0.83 mmol) and sodium triacetoxy borohydride (0.176 g, 0.83 mmol). The reaction mixture was stirred at room temperature for 24 h under a nitrogen atmosphere. Sodium hydroxide (1N, 15 mL) was added to the reaction mixture and was stirred for 1h. The organic layer was removed under reduced pressure and dichloromethane was added. The layers were partitioned and the aqueous layer was extracted with dichloromethane (200 mL). The combined organic layers were dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude material was purified by flash chromatography on silica gel using 10% methanol in dichloromethane (20 min), 15% methanol in dichloromethane (10 min), 20% methanol in dichloromethane (10 min) and 50% methanol in dichloromethane (8 min) as the eluent. The column afforded 0.074 g (25%) of pure *N*2-(4-{4-amino-1-[1-(1*H*-4-imidazolylmethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.446 (s, 1H), 8.252 (s, 1H), 8.126-8.1082 (d, 1H, *J* = 8.16 Hz), 7.7198-7.7 (d, 1H, *J* = 7.92 Hz), 7.6-7.569 (m, 2H), 7.35-7.298 (m, 4H), 7.171-7.134 (m, 1H), 6.946 (s, 1H), 5.422-5.385 (m, 1H), 4.043 (s, 3H), 3.961 (s, 3H), 3.691 (s, 2H), 3.175-3.162 (m, 2H), 2.9-2.883 (m, 3H), 2.385-2.332 (m, 2H); LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3μm particle size, 33 x 4.6mm; 70 % 50 mM ammonium acetate in water to 95% acetonitrile over 6 min, 0.8 to 0.5 mL/min) R_t 2.13 min (100%), MH^+ 563.3.

Example 858: *N*2-[4-(4-amino-1-{1-[(3-methyl-1*H*-4-pyrazolyl)methyl]tetrahydro-1*H*-3-pyrrolyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide

A suspension of *N*2-[4-(4-amino-1-tetrahydro-1*H*-3-pyrrolyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide (0.200 g, 0.415 mmol) in dichloroethane (5 mL) was treated with 3-methyl-1*H*-pyrazol-4-carboxaldehyde (0.091 g, 0.83 mmol) and sodium triacetoxy borohydride (0.176 g, 0.83 mmol). The reaction mixture was stirred at room temperature for 24 h under a nitrogen atmosphere. Sodium hydroxide (1N, 15 mL)

was added to the reaction mixture and was stirred for 1h. The organic layer was removed under reduced pressure and dichloromethane was added. The layers were partitioned and the aqueous layer was extracted with dichloromethane (100 mL) and ethyl acetate (100 mL). The combined organic layers were dried over magnesium sulfate, filtered and evaporated under reduced pressure. The crude material was purified by flash chromatography on silica gel using 10% methanol in dichloromethane (15 min), 15% methanol in dichloromethane (10 min), 20% methanol in dichloromethane (10 min) and 50% methanol in dichloromethane (8 min) as the eluent. The column afforded 0.106 g (44%) of pure *N*2-[4-(4-amino-1-{1-[(3-methyl-1*H*-4-pyrazolyl)methyl]tetrahydro-1*H*-3-pyrrolyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.446 (s, 1H), 8.247 (s, 1H), 8.1275-8.1071 (d, 1H, J = 8.16 Hz), 7.72-7.7003 (d, 1H, J = 7.96 Hz), 7.6004-7.5793 (d, 1H, J = 8.44 Hz), 7.398-7.286 (m, 5H), 7.172-7.134 (m, 1H), 5.379 (m, 1H), 4.0443 (s, 3H), 3.962 (s, 3H), 3.492 (m, 2H), 3.1 (m, 1H), 2.75 (m, 3H), 2.352-2.335 (m, 2H), 1.909 (s, 3H); LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3μm particle size, 33 x 4.6mm; 70 % 50 mM ammonium acetate in water to 95% acetonitrile over 6 min, 0.8 to 0.5 mL/min) R_t 2.17 min (100%), MH^+ 577.3.

Example 859: *N*2-(4-{4-amino-1-[(3*R*)-1-methyltetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

*N*2-(4-{4-amino-1-[(3*R*)-1-methyltetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine was prepared from (*S*)-(-)-3-pyrrolidinol in a manner analogous to that used for the preparation of *rac*-*N*2-{4-[4-Amino-1-(1-methyltetrahydro-1*H*-3-pyrrolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}-5,7-dimethyl-1,3-benzoxazol-2-amine. The compound was formed as a white solid (0.195 g, 53%). ^{1}H NMR (DMSO-d_6, 400 MHz) ^{1}H NMR (DMSO-d_6, 400 MHz) 2.31-2.35 (m, 2 H), 2.32 (s, 3 H), 2.35 (s, 3 H), 2.40 (s, 3 H), 2.70-2.77 (m, 3 H), 3.05 (t, 1 H), 5.40 (m, 1 H), 6.80 (s, 1 H), 7.11 (s, 1 H), 7.66 (d, 2 H), 7.93 (d, 2 H), 8.24 (s, 1 H), 10.85 (s, 1 H); RP-HPLC Rt 11.090 min, 99% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate,

buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μm, 150 x 3.9 mm column); *m/z* 455 (MH^+).

Example 860: *N*2-(4-{4-amino-1-[(3*S*)-1-methyltetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

*N*2-(4-{4-amino-1-[(3*S*)-1-methyltetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine was prepared from (*R*)-(-)-3-pyrrolidinol in a manner analogous to that used for the preparation of *rac*-*N*2-{4-[4-Amino-1-(1-methyltetrahydro-1*H*-3-pyrrolyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}-5,7-dimethyl-1,3-benzoxazol-2-amine. The compound was formed as a white solid (0.126 g, 20%). ^{1}H NMR (DMSO-d_6, 400 MHz) ^{1}H NMR (DMSO-d_6, 400 MHz) 2.31-2.35 (m, 2 H), 2.31 (s, 3 H), 2.35 (s, 3 H), 2.40 (s, 3 H), 2.67-2.76 (m, 3 H), 3.05 (t, 1 H), 5.40 (m, 1 H), 6.80 (s, 1 H), 7.11 (s, 1 H), 7.66 (d, 2 H), 7.93 (d, 2 H), 8.24 (s, 1 H), 10.84 (s, 1 H); RP-HPLC Rt 11.129 min, 100% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μm, 150 x 3.9 mm column); *m/z* 455 (MH^+).

Example 861: *rac*- *N*2-(4-{4-amino-1-[1-(2-methoxyethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-7-isopropyl-5-methyl-1,3-benzoxazol-2-amine

rac-*N*2-(4-{4-Amino-1-[1-(2-methoxyethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-7-isopropyl-1,3-benzoxazol-2-amine was prepared from *rac*-3-iodo-1-[1-(2-methoxyethyl)tetrahydro-1*H*-3-pyrrolyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.200 g, 0.515 mmol) and *N*2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-7-isopropyl-1,3-benzoxazol-2-amine (0.244 g, 0.644 mmol) in a manner similar to that used for the preparation of *cis*-*N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-fluorophenyl)-1,3-benzoxazol-2-amine. The compound was formed as an off-white solid (0.067 g, 25%). ^{1}H NMR (DMSO-d_6, 400 MHz) 1.361 (d, 6 H), 2.30 (m, 2 H), 2.66 (m, 2 H), 2.76-2.83 (m, 3 H), 3.17 (t, 1 H), 3.24 (s, 3 H), 3.38 (m, 1 H), 3.45 (t, 2 H), 5.37 (m, 1 H), 7.04 (d, 1 H), 7.18 (t, 1 H), 7.32 (d, 2 H), 7.67 (d, 2 H),

7.95 (d, 2 H), 8.24 (s, 1 H), 10.88 (s, 1 H); RP-HPLC Rt 12.337 min, 94% purity (5% to 85% acetonitrile/0.1M aqueous ammonium acetate, buffered to pH 4.5, over 20 min at 1mL/min; λ = 254 nm; Deltapak C18, 300 Å, 5 μm, 150 x 3.9 mm column); *m/z* 513 (MH^+).

Example 861: *cis*-Ethyl 4-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-cyclohexanecarboxylate

3-Iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.52 g, 2.0 mmol), ethyl 4-hydroxycyclohexanecarboxylate (0.806 mL, 5.0 mmol, triphenylphosphine (1.05 g, 4.0 mmol), diethyl azodicarboxylate (0.628 mL, 4.0 mmol) were suspended in tetrahydrofuran (15 mL), and the mixture was stirred at ambient temperature under a gentle flow of nitrogen for 48 h. The mixture was diluted with water (50 mL), and extracted with ethyl acetate (3 x 50 mL). The organic fractions were combined, dried over magnesium sulfate, filtered, and concentrated. The residue was partially purified by flash column chromatography (100% ethyl acetate) to afford ethyl 4-(4-amino-5-iodo-7*H*-pyrrolo[3,4-*d*]pyrimidin-7-yl)-1-cyclohexanecarboxylate as a mixture of *cis*- and *trans*-diastereomers, along with triphenylphosphine oxide. Repurification of the mixture by flash column chromatography on silica gel deactivated with triethylamine (0.5 % methanol/dichloromethane as eluant) afforded the desired *cis*-ethyl 4-(4-amino-5-iodo-7*H*-pyrrolo[3,4-*d*]pyrimidin-7-yl)-1-cyclohexanecarboxylate as a yellow solid (0.260 g, 0.625 mmol): RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5 μ Hypersil HS C18, 250 x 4.6 mm column) R_t 9.55 min; MS $(MH)^+$ 416.

cis-Ethyl 4-(4-amino-5-iodo-7*H*-pyrrolo[3,4-*d*]pyrimidin-7-yl)-1-cyclohexanecarboxylate (0.10 g, 0.24 mmol) was combined with *N*-(5,7-dimethyl-1,3-benzoxazol-2-yl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.088 g, 0.24 mmol), sodium carbonate (0.064 g, 0.60 mmol), tetrakis(triphenylphosphine)-palladium (0) (0.014 g, 0.012 mmol), ethylene glycol dimethyl ether (2 mL) and water (1 mL), and the mixture was heated at 85 °C in a resealable Schlenk tube for 14 h. The reaction mixture was cooled to ambient temperature, diluted with water (10 mL), and extracted with 10% methanol dichloromethane (3 x 20 mL). The organic fractions were combined, dried over

magnesium sulfate, filtered, and concentrated. Purification of the product by flash column chromatography on silica gel deactivated with triethylamine (2.5% methanol/dichloromethane as eluant) afforded ***cis***-ethyl 4-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-cyclohexanecarboxylate as a white solid (0.040 g, 0.076 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5 μ Hypersil HS C18, 250 x 4.6 mm column) R_t 12.63 min; . ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.85 (s, 1H), 8.23 (s, 1H), 7.92 (d, 2H), 7.64 (d, 2H), 7.11 (s, 1H), 6.80 (s, 1H), 4.66 (m, 1H), 4.10 (qt, 2H), 3.27 (m, 1H), 2.40 (s, 3H), 2.35 (s, 3H), 2.08 (m, 6H), 1.61 (m, 2H), 1.20 (t, 3H).

Example 862: *cis*-Methyl 4-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-cyclohexanecarboxylate

cis-Ethyl 4-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-cyclohexanecarboxylate (0.030 g, 0.057 mmol), sodium methoxide (0.0033 g, 0.063 mmol) and methanol (2 mL) were combined and heated in a resealable Schlenk tube for 48 h at 75 °C. Purification of the product by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 15.6-16.5 min) afforded ***cis***-methyl 4-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-cyclohexanecarboxylate as a white powder (0.010 g, 0.020 mmol): RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5 μ Hypersil HS C18, 250 x 4.6 mm column) R_t 11.82 min; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.85 (s, 1H), 8.23 (s, 1H), 7.92 (d, 2H), 7.65 (d, 2H), 7.12 (s, 1H), 6.80 (s, 1H), 4.67 (m, 1H), 3.63 (s, 3H), 3.27 (m, 1H), 2.40 (s, 3H), 2.35 (s, 3H), 2.07 (m, 6H), 1.61 (m, 2H).

Example 863: *cis*-4-(4-Amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-cyclohexanecarboxylic acid

cis-Ethyl 4-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-cyclohexanecarboxylate (0.10 g, 0.19 mmol), aqueous sodium hydroxide (1 M, 2 mL, 2 mmol), and methanol (2 mL) were combined and heated under an air condenser at 70 °C for 14 h. The residue was acidified with aqueous hydrochloric acid (3 M, 2 mL, 6 mmol), and extracted with 10% methanol/dichloromethane (3 x 20 mL). The combined organic fractions were dried over magnesium sulfate, filtered, and concentrated. Purification of the product by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 8.8-10.9 min) afforded *cis*-4-(4-Amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-cyclohexanecarboxylic acid as a cream-colored powder (0.026 g, 0.052 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5 μ Hypersil HS C18, 250 x 4.6 mm column) R_t 9.03 min; MS $(MH)^+$ 498.

Example 864: *cis*-1-[4-(4-Methylpiperazino)cyclohexyl]-3-[4-(2-pyrimidinylamino)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

4-Bromoaniline (0.300 g, 1.74 mmol) and 2-chloropyrimidine (0.200 g, 1.74 mmol) were heated neat at 150 °C in a 25 mL flask for 2 h. The reaction mixture was cooled to ambient temperature, and purification of the residue by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 13.8-15.9 min) afforded *N*-(4-bromophenyl)-*N*-(2-pyrimidinyl)amine as a yellow solid (0.135 g, 0.54 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5 μ Hypersil HS C18, 250 x 4.6 mm column) R_t 11.08 min; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.78 (s, 1H), 8.50 (d, 2H), 7.76 (d, 2H), 7.45 (d, 2H), 6.87 (t, 1H).

N-(4-Bromophenyl)-*N*-(2-pyrimidinyl)amine was converted to the title compound using a procedure similar to the one described in the preparation of *cis*-*N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-4-ethyl-1,3-thiazol-2-amine. Purification of the product

by preparative HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 20 min at 21 mL/min using an 8 μ Hypersil HS C18, 250 x 21 mm column, R_t 4.0-5.0 min) afforded *cis*-1-[4-(4-methylpiperazino)cyclohexyl]-3-[4-(2-pyrimidinylamino)phenyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine as a white powder (0.095 g, 0.196 mmol); RP-HPLC (25 to 100 % acetonitrile in 0.1 M aqueous ammonium acetate over 10 min at 1 mL/min using a 5 μ Hypersil HS C18, 250 x 4.6 mm column) R_t 5.38 min; MS $(MH)^+$ 485.

Example 865: *N*2-(4-{4-amino-1-[2-(4-methylpiperazino)-4-pyridyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1*H*-2-indolecarboxamide acetate

A. 1-(2-chloro-4-pyridyl)-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

A solution of 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (4.12 g, 0.016 mol) in *N,N*-dimethylformamide (50 mL) was reacted with 60% sodium hydride in oil (0.75 g, 0.019 mol) at ambient temperature. The mixture was stirred for 15 minutes, and 2-chloro-4-nitropyridine (3.00 g, 0.019 mol) was added. The mixture was heated at 100° C for 18 hours. The mixture was cooled to room temperature and the precipitate was filtered, washing with *N,N*-dimethylformamide (20 mL), and then slurried in ethyl acetate (50 mL) for four hours. The solid was filtered and dried *in vacuo* to give 1-(2-chloro-4-pyridyl)-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (2.39 g, 0.009 mol) as a tan solid:

^{1}H NMR (DMSO-d_6, 400MHz) δ 8.52 (d, 1H), 8.43 (s, 1H), 8.40 (d, 1H), 8.25 (dd, 1H); RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) R_t 10.29 min.;

MS: MH^+ 373.

B. *N*2-{4-[4-amino-1-(2-chloro-4-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide

A suspension of 1-(2-chloro-4-pyridyl)-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.95 g, 0.00256 mol) in dimethoxyethane (30 mL) and water (60 mL) was reacted with *N*2-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-methyl-1*H*-2-indolecarboxamide (1.14 g, 0.00281 mol), sodium carbonate (0.68 g,

0.00640 mol) and tetrakis (triphenylphosphine)palladium (0) (0.30 g, 0.00026 mol) at 80° C for 3 days. The solid was filtered and washed with water. The solid was triturated with ethyl acetate (75 mL) for 6 hours and filtered, washing with ethyl acetate (20 mL). The solid was then triturated with methanol (75 mL) for 6 hours and filtered, washing with methanol(20 mL). The solid was dried *in vacuo* to give crude *N*2-{4-[4-amino-1-(2-chloro-4-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide (0.672 g, 0.00128 mol) as a tan solid:

^{1}H NMR (DMSO-d_6, 400MHz) δ 9.48 (s, 1H) 8.55-8.58 (m, 2H), 8.50 (s, 1H), 8.44 (dd, 1H), 8.21 (d, 1H), 7.72 (d, 1H), 7.60 (d, 1H), 7.49 (d, 1H), 7.43 (dd, 1H), 7.31-7.38 (m, 2H), 7.16 (t, 1H), 4.05 (s, 3H), 4.00 (s, 1H);

RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, isocratic at 95% for 3 min., 1mL/min) R_t 12.70 min.;

MS: MH^+ 525.

C. *N*2-(4-{4-amino-1-[2-(4-methylpiperazino)-4-pyridyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1*H*-2-indolecarboxamide acetate

A suspension of *N*2-{4-[4-amino-1-(2-chloro-4-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide (0.120 g, 0.00023 mol) in 1-methylpiperazine (5 mL) heated at 120° C for 5 days. The solvent was removed *in vacuo* and the residue was slurried in diethyl ether (25 mL) for 4 hours. The mixture was filtered, washing with diethyl ether (105 mL) and dried *in vacuo*. The crude material was purified by preparative RP-HPLC (Rainin C18, 8mm, 300 A, 25 cm; 40% isocratic for five minutes, then 40%-100% acetonitrile - 0.1M ammonium acetate over 30 min, 21 mL/min). The acetonitrile was removed in vacuo and the aqueous mixture was lyopholyzed to give *N*2-(4-{4-amino-1-[2-(4-methylpiperazino)-4-pyridyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1*H*-2-indolecarboxamide acetate (0.030 g, 0.00005 mol) as a white solid.

^{1}H NMR (DMSO-d_6, 400MHz) δ 9.47 (s, 1H), 8.44 (s, 1H), 8.12 (d, 1H), 7.77 (s, 1H), 7.72 (d, 1H), 7.68 (d, 1H), 7.60 (d, 1H), 7.30-7.37 (m, 3H), 7.26 (d, 1H), 7.15 (t, 1H), 4.06 (s, 3H), 3.50-3.58 (m, 4H), 2.38-2.46 (m, 4H), 2.24 (s, 3H), 1.91 (s, 3H);

RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 15.33 min.;
MS: MH^+ 575.

Example 866: *N*2-{4-[4-amino-1-(2-morpholino-4-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide

A suspension of *N*2-{4-[4-amino-1-(2-chloro-4-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide (0.120 g, 0.00023 mol) and morpholine (10 mL) was heated at 100° C for 6 days. The solvent was removed *in vacuo* and the residue was slurried in water (25 mL) for 4 hours. The mixture was filtered and the crude solid was purified by preparative RP-HPLC (Rainin C18, 8mm, 300 A, 25 cm; 35%-80% acetonitrile - 0.050 M ammonium acetate over 20 min, 21 ml/min). The acetonitrile was removed in vacuo and the aqueous mixture was lyopholyzed to give *N*2-{4-[4-amino-1-(2-morpholino-4-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide (0.048 g, 0.00008 mol) as a white solid.
^{1}H NMR (DMSO-d_6, 400MHz) δ 948 (s, 1H), 8.44 (s, 1H), 8.27 (d, 1H), 8.18 (d, 1H), 7.82 (d, 1H), 7.74 (dd, 1H), 7.72 (d, 1H), 7.60 (d, 1H), 7.46 (d, 1H), 7.41 (dd, 1H), 7.36 (s,1H), 7.34 (t, 1H), 7.16 (t, 1H), 4.05 (s, 3H), 3.99 (s, 3H), 3.72-3.78 (m, 4H), 3.49-3.56 (m, 4H);
RP-HPLC (Delta Pak C18, 5μm, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 20 min, 1mL/min) R_t 17.89 min.;
MS: MH^+ 576.

Example 867: (*S*)-*N*2-(4-{4-amino-1-[1-(2-methoxyethyl)-3-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

A. (*R*)-*tert*-butyl 3-hydroxy-1-piperidinecarboxylate

A mixture of (*R*)-3-hydroxy piperidine hydrochloride (10 g, 0.073 mol), di-*tert*-butyl dicarbonate (20 g, 0.091 mol) and sodium carbonate (19 g, 0.182 mol) in dioxane (80 mL) and water (80 mL) was stirred at room temperature under an

atmosphere of nitrogen for 18 hours. The organic solvent was removed under the reduced pressure. The aqueous layer was extracted with diethyl ether (2 x 200 mL). The organic layer was washed with brine and dried over magnesium sulfate. The solvent was removed under the reduced pressure to yield clear oil of (*R*)-*tert*-butyl 3-hydroxy-1-piperidinecarboxylate (17.6 g, 0.087 mol). The crude product was carried to the next reaction.

^{1}H NMR (Chloroform-*d*, 400 MHz) δ 3.76 (m, 1H), 3.67 (br, 1H), 3.55 (br, 1H), 2.92 (m, 2H), 2.75 (s, 1H), 1.85 (br, 1H), 1.72 (br, 1H), 1.46 (br, 11H)

GC-MS: MH^+ 202

B. (*S*)-*Tert*-butyl 3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-piperidinecarboxylate

To a mixture of 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (2 g, 0.0077 mol), (*R*)-*tert*-butyl 3-hydroxy-1-piperidinecarboxylate (2.3 g, 0.012 mol), and triphenylphosphine (3 g, 0.012 mol) in tetrahydrofuran (70 mL), diethyl azodicarboxylate (2 g, 0.012 mol) was added at 0 °C. The mixture was stirred at room temperature under an atmosphere of nitrogen for 2 days. In order to complete the reaction, additional (*R*)-*tert*-butyl 3-hydroxy-1-piperidinecarboxylate (0.62 g, 0.003 mol), and triphenylphosphine (0.81 g, 0.012 mol), and diethyl azodicarboxylate (0.6 g, 0.003 mol) were added to the mixture. The mixture was stirred at room temperature under an atmosphere of nitrogen for additional 18 hours. The solvent was removed under the reduced pressure to yield crude (*S*)- *tert*-butyl 3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-piperidinecarboxylate, which was used crude for the next reaction.

RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 10.0 min.

MS: MH^+ 445

C. (*S*)-3-iodo-1-(3-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate

To a mixture of (*S*)- *tert*-butyl 3-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-1-piperidinecarboxylate (3.4 g, 0.0077 mol) in acetone (80mL)

was added an aqueous 6N solution of hydrogen chloride (20 mL) at room temperature. The mixture was stirred at 45 °C for 4 hours, then at room temperature for 18 hours. Acetone was removed under reduced pressure, and the aqueous layer was washed with toluene (2 x 20 mL) and dichloromethane (2 x 20 mL). The aqueous layer was basified with an aqueous 5N solution of sodium hydroxide (25 mL) at 0 °C. The aqueous layers were concentrated to dryness, and the residue was purified by RP-HPLC (Hypersilprep HS C18, 8μm, 250 x 21.1 mm; 2% - 30% over 15 min with 0.1 M ammonium acetate, 21mL/min) to yield (*S*)-3-iodo-1-(3-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate (0.75 g, 0.0019 mol). RP-HPLC (Hypersil C18, 5μm, 250 x 4.6 mm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 8.2 min.
MS: MH^+ 345

D. (*S*)-3-iodo-1-[1-(2-methoxyethyl)-3-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

To a mixture of (*S*)-3-iodo-1-(3-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate (0.75 g, 0.0019 mol) and potassium carbonate (0.77 g, 0.00568mol) in *N,N*-dimethylformamide (30 mL) were added 2-bromoethyl methyl ether (0.27 g, 0.0019 mol) and potassium iodide (0.0016 g, 0.000095 mol) at room temperature. The mixture was stirred at 65 °C under an atmosphere of nitrogen for 16 hours. The reaction mixture was cooled to room temperature, and 2-bromoethyl methyl ether (0.27 g, 0.0019 mol) and potassium iodide (0.0016 g, 0.000095 mol) were added. The mixture was stirred at 65 °C under an atmosphere of nitrogen for 4 hours. The solvent was removed under the reduced pressure. The residue was partitioned between saturated sodium bicarbonate solution (25 mL) and dichloromethane (50 mL). The aqueous layer was extracted with dichloromethane (4 x 50 mL). The solvents were evaporated under the reduced pressure, and the residue was purified by RP-HPLC (Hypersilprep HS C18, 8μm, 250 x 21.1 mm; 2% - 30% over 15 min with 0.1 M ammonium acetate, 21mL/min) to (*S*)-3-iodo-1-[1-(2-methoxyethyl)-3-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate (0.64 g, 0.0014 mol). RP-HPLC (Hypersil C18, 5μm, 250 x 4.6 mm; 5%-85% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 8.9 min.

MS: MH^+ 403

E. (*S*)-*N*2-(4-{4-amino-1-[1-(2-methoxyethyl)-3-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

A mixture of (*S*)-3-iodo-1-[1-(2-methoxyethyl)-3-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine acetate (0.64 g, 0.0014 mol), *N*-(5,7-dimethyl-1,3-benzoxazol-2-yl)-*N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]amine (0.64 g, 0.00175 mol, 1.2 eq.), tetrakis(triphenylphosphine)palladium (0.081 g, 0.00007 mol) and sodium carbonate (0.37 g, 0.0035 mol) in *N,N*-dimethylformamide (15 mL) and water (7 mL) was heated at 80°C for 16 hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature, and the solvent was removed under the reduced pressure. The residue was partitioned between water (25 mL) and dichloromethane (50 mL). The aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic extracts were washed with brine and dried over magnesium sulfate. The solvents were evaporated under the reduced pressure to leave a brownish oil, which was purified by flash column chromatography on silica using 2 % - 10 % methanol / dichloromethane as a mobile phase to give (*S*)-*N*2-(4-{4-amino-1-[1-(2-methoxyethyl)-3-piperidyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine (0.60 g, 0.0012mol).

^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.85 (s, 1H), 8.25 (s, 1H), 7.93 (d, 2H), 7.65 (d, 2H), 7.11 (s, 1H), 6.80 (s, 1H), 4.77 (br, 1H), 3.36 (m, 2H), 3.25 (s, 3H), 3.04 (br, 1H), 2.90 (br, 1H), 2.55 (br, 2H), 2.54 (br, 1H), 2.40 (s, 3H), 2.35 (s, 3H), 2.02 (br, 3H), 1.80 (br, 1H), 1.70 (br, 1H).

RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 11.9 min.

MS: MH^+ 513

Example 868: *Cis*-2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)-1,3-benzoxazole-5-carboxamide triacetate

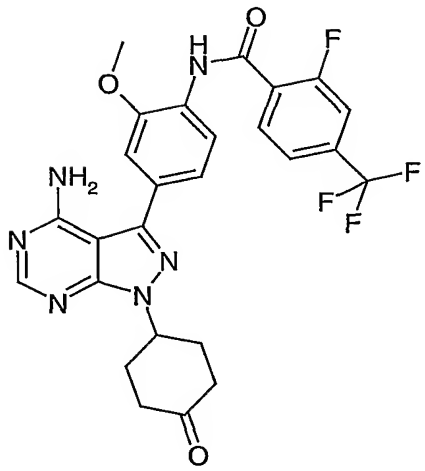
To a mixture of *cis*-2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)-1,3-benzoxazole-5-carbonitrile triacetate (0.18 g, 0.00025 mol) in dioxane (2 mL) were added a 2N aqueous solution of sodium hydroxide (1.25 mL, 0.0025 mol) and water (0.75 mL). The mixture was stirred at room temperature for 2 minutes under the atmosphere of nitrogen before adding 30 % hydrogen peroxide solution (0.2 mL). The mixture was refluxed for 5 hours, then stirred at room temperature for 18 hours. More 30 % hydrogen peroxide solution (0.2 mL) was added to the mixture before refluxing for additional 6 hours, then stirred at room temperature for 2 days. The organic solvent was removed under reduced pressure, and 5 % citric acid solution was added to maintain pH 7. The aqueous layer was removed under reduced pressure, and the crude was purified by RP-HPLC (Hypersilprep HS C18, 8μm, 250 x 21.1 mm; 5% - 100 % over 25 min with 0.1 M ammonium acetate, 21mL/min) to give *cis*-2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}anilino)-1,3-benzoxazole-5-carboxamide triacetate (0.11 g, 0.00015 mol).

^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.30 (s, 1H), 8.15 (s, 1H), 8.00 (m, 3H), 7.75 (m, 1H), 7.70(m, 2H), 7.60 (d, 1H), 7.35 (br, 1H), 4.80 (br, 1H), 2.50 (br, 2H), 2.40 (br, 4H), 2.25 (br, 4H), 2.15 (s, 3H), 2.10 (br, 3H), 1.90 (s, 9H), 1.70 (br, 2H), 1.60 (br, 2H).

RP-HPLC (Delta Pak C18, 5µm, 300A, 15 cm; 5%-95% acetonitrile – 0.1M ammonium acetate over 10 min, 1mL/min) Rt 8.2 min.

MS: MH^+ 567

Example 869: *N*1-{4-[4-Amino-1-(4-oxocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide

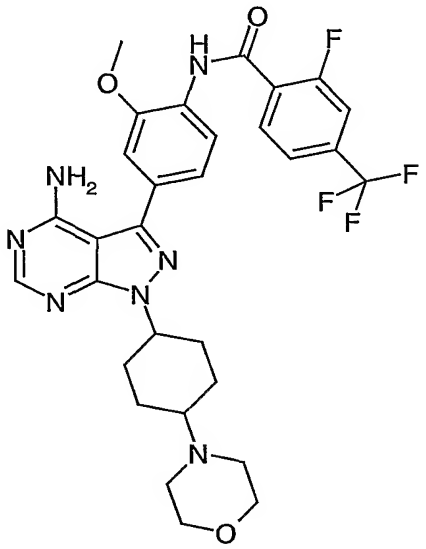


A solution of 2-fluoro-4-trifluoromethyl-1-benzenecarbonyl chloride (0.87 g, 3.83 mmol) in dichloromethane (5 mL) was added into a mixture of pyridine (15 mL) and 4-[4-amino-3-(4-amino-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-cyclohexanone (1.00 g, 2.56 mmol) in dichloromethane (5 mL) at 0°C over 5 minutes. The mixture was stirred at 0°C for 10 minutes and at ambient temperature overnight. The solvent was removed under reduced pressure. The residue was partitioned between water and dichloromethane. The dichloromethane layer was washed with saturated aqueous ammonium chloride twice and saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered and evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography on silica using Isco system to provide *N*1-{4-[4-amino-1-(4-oxocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide (0.95 g, 1.76 mmol) as a white solid: ^{1}H NMR (DMSO-d_6, 400MHz) δ 9.90 (dd, 1H), 8.30(d, 1H), 8.28 (s, 1H), 7.99 (t, 1H), 7.89 (d, 1H), 7.75 (d, 1H), 7.34 (s, 1H), 7.30 (d, 1H), 6.90 (br, 2H), 5.27 (m, 1H), 3.94 (s, 3H), 2.70 (m, 2H), 2.47 (m, 4H), 2.17 (m, 2H); RP-HPLC (Hitachi HPLC, Hypersil C18, 5μm, 100A, 250x4.6mm; 25%-100% acetonitrile - 0.05M ammonium acetate over 10 min, 1mL/min) R_t 9.23 min. MS: MH^+ 543.

Example 870: Cis-*N*1-{4-[4-amino-1-(4-morpholinocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide; and

Example 871: Trans-*N*1-{4-[4-amino-1-(4-morpholinocyclohexyl)-1*H*-pyrazolo[3,4-

d]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide



Morpholine (0.08 mL, 0.93 mmol) was added into a mixture of *N*1-{4-[4-amino-1-(4-oxocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide (0.42 g, 0.78 mmol) and acetic acid (0.11 mL, 1.86 mmol) in dichloroethane (25 mL). The mixture was stirred at ambient temperature for 10 minutes. Sodium triacetoxyborohydride (0.23 g, 1.09 mmol) was added and the mixture was stirred at ambient temperature overnight. Water (6 mL) was added followed by sodium bicarbonate (0.38 g, 4.53 mmol). The mixture was stirred for 1 hour and the organic layer was separated. The aqueous layer was extracted with dichloromethane (20 mL). The combine organics were dried over magnesium sulfate, filtered and evaporated under reduced pressure to give a crude product. The crude product was purified by flash column chromatography on silica using Isco system to provide cis-*N*1-{4-[4-amino-1-(4-morpholinocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide (0.23 g, 0.37 mmol) and trans-*N*1-{4-[4-amino-1-(4-morpholinocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide (0.09 g, 0.14 mmol) as white solids.

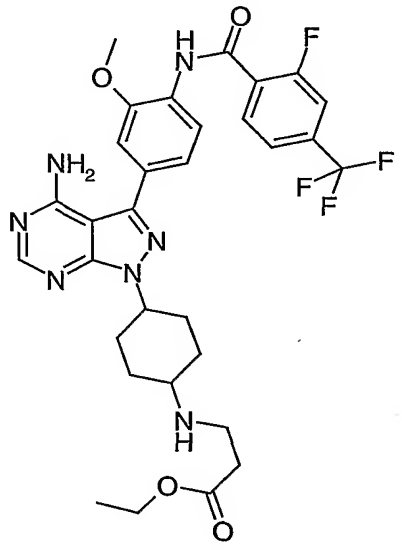
Data for cis-*N*1-{4-[4-amino-1-(4-morpholinocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide: ^{1}H NMR (DMSO-d_6, 400MHz) δ 9.91 (dd, 1H), 8.30(d, 1H), 8.24 (s, 1H), 8.00 (t, 1H), 7.89 (d, 1H), 7.75 (d, 1H), 7.33 (s, 1H), 7.30 (d, 1H), 6.90 (br, 2H), 4.83 (m, 1H),

3.94 (s, 3H), 3.62 (br, 4H), 1.57-2.55 (m, 10H); MS: MH^+ 614.

Data for trans-*N*1-{4-[4-amino-1-(4-morpholinocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide: ^{1}H NMR (DMSO-d_6, 400MHz) δ 9.90 (dd, 1H), 8.30(d, 1H), 8.24 (s, 1H), 7.99 (t, 1H), 7.89 (d, 1H), 7.75 (d, 1H), 7.32 (s, 1H), 7.29 (s, 1H), 4.67 (m, 1H), 3.94 (s, 3H), 3.59 (br, 4H), 1.48-2.69 (m, 10H); MS: MH^+ 614.

Example 872: *Cis*-ethyl 3-({4-[4-amino-3-(4-{[2-fluoro-4-trifluoromethylbenzoyl]amino}-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl}amino)propanoate; and

Example 873: *Trans*-ethyl 3-({4-[4-amino-3-(4-{[2-fluoro-4-trifluoromethylbenzoyl]amino}-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl}amino)propanoate



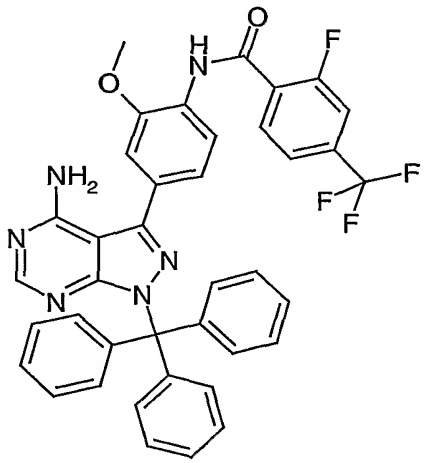
A similar procedure to the preparation of cis-*N*1-{4-[4-amino-1-(4-morpholinocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide and trans-*N*1-{4-[4-amino-1-(4-morpholinocyclohexyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide yielded cis-ethyl 3-({4-[4-amino-3-(4-{[2-fluoro-4-trifluoromethylbenzoyl]amino}-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl}amino)propanoate and trans-ethyl 3-({4-[4-amino-3-(4-{[2-fluoro-4-trifluoromethylbenzoyl]amino}-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-

1-yl]cyclohexyl}amino)propanoate as white solids.

Data for cis-ethyl 3-({4-[4-amino-3-(4-{[2-fluoro-4-trifluoromethylbenzoyl]amino}-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl}amino)propanoate: ^{1}H NMR (DMSO-d_6, 400MHz) δ 9.90 (dd, 1H), 8.30(d, 1H), 8.23 (s, 1H), 8.00 (t, 1H), 7.89 (d, 1H), 7.75 (d, 1H), 7.33 (s, 1H), 7.30 (d, 1H), 6.90 (br, 2H), 4.37 (m, 1H), 4.08 (q, 2H), 3.94 (s, 3H), 2.76 (m, 2H), 2.32 (m, 2H), 1.88 (m, 2H), 1.67 (m, 4H), 1.16 (t, 3H); RP-HPLC (Hitachi HPLC, Hypersil C18, 5μm, 100A, 250x4.6mm; 25%-100% acetonitrile - 0.05M ammonium acetate over 10 min, 1mL/min) R_t 7.92 min. MS: MH^+ 644.

Data for trans-ethyl 3-({4-[4-amino-3-(4-{[2-fluoro-4-trifluoromethylbenzoyl]amino}-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl}amino)propanoate: ^{1}H NMR (DMSO-d_6, 400MHz) δ 9.89 (dd, 1H), 8.30(d, 1H), 8.24 (s, 1H), 8.00 (t, 1H), 7.89 (d, 1H), 7.75 (d, 1H), 7.32 (s, 1H), 7.29 (d, 1H), 6.90 (br, 2H), 4.68 (m, 1H), 4.08 (q, 2H), 3.94 (s, 3H), 2.82 (m, 2H), 2.46 (m, 5H), 1.91-2.07 (m, 6H), 1.18 (t, 3H); RP-HPLC (Hitachi HPLC, Hypersil C18, 5μm, 100A, 250x4.6mm, 25%-100% acetonitrile - 0.05M ammonium acetate over 10 min, 1mL/min) R_t 7.69 min. MS: MH^+ 644.

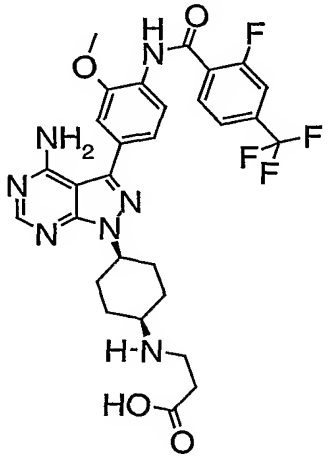
Example 874: *N*1-[4-(4-Amino-1-trityl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-trifluoromethylbenzamide



A mixture of 3-iodo-1-trityl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.10 g, 0.19 mmol), *N*1-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-fluoro-4-trifluoromethylbenzamide (0.13 g, 0.29 mmol),

tetrakis(triphenylphosphine)palladium(0) (0.01 g, 0.01 mmol) and sodium carbonate monohydrate (0.06 mg, 0.48 mmol) in water (2 mL) and ethylene glycol dimethyl ether (4 mL) was heated at 85°C overnight. The solvents were removed under reduced pressure. Water was added into the residue and the mixture was extracted with ethyl acetate three times. The combined organics were washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered and evaporated to yield a brown solid which was purified by flash column chromatography on silica using Isco system to provide *N*1-[4-(4-amino-1-trityl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-trifluoromethylbenzamide (0.12 g, 0.17 mmol) as a white solid: ^{1}H NMR (DMSO-d_6, 400MHz) δ 9.89 (dd, 1H), 8.25(d, 1H), 8.28 (s, 1H), 8.00 (t, 1H), 7.94 (s, 1H), 7.88 (d, 1H), 7.73 (d, 1H), 7.24 (m, 15H), 3.90 (s, 3H); MS: MH^+ 689.

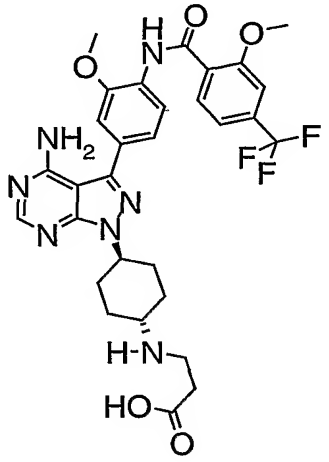
Example 875: Cis-3-({4-[4-amino-3-(4-{[2-fluoro-4-trifluoromethylbenzoyl]amino}-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl}amino)propanoic acid



A mixture of cis-ethyl 3-({4-[4-amino-3-(4-{[2-fluoro-4-trifluoromethylbenzoyl]amino}-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl}amino)propanoate (0.23 g, 0.36 mmol), p-dioxane (15 mL), potassium hydroxide (0.10 g, 1.81 mmol) and water (1.5 mL) were heated at 80°C for 3 hours. The solvents were evaporated and the residue was purified by preparative HPLC to yield cis-3-({4-[4-amino-3-(4-{[2-fluoro-4-trifluoromethylbenzoyl]amino}-3-

methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl}amino)propanoic acid (0.11 g, 0.18 mmol) as a white solid: ^{1}H NMR (DMSO-d_6, 400MHz) δ 9.91 (dd, 1H), 8.31 (d, 1H), 8.25 (s, 1H), 8.00 (t, 1H), 7.89 (d, 1H), 7.75 (d, 1H), 7.35 (s, 1H), 7.32 (s, 1H), 6.89 (br, 2H), 4.79 (m, 1H), 3.95 (s, 3H), 2.46-3.00 (m, 7H), 2.29 (m, 2H), 1.91 (m, 2H), 1.80 (m, 2H); RP-HPLC (Hitachi HPLC, Hypersil C18, 5μm, 100A, 250x4.6mm; 25%-100% acetonitrile - 0.05M ammonium acetate over 10 min, 1mL/min) R_t 6.06 min. MS: MH^+ 616.

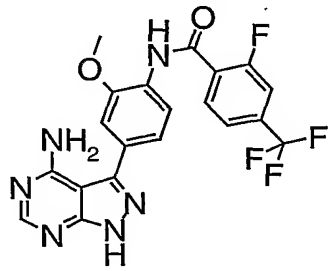
Example 876: Trans-3-({4-[4-amino-3-(3-methoxy-4-{[2-methoxy-4-trifluoromethylbenzoyl]amino}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl}amino)propanoic acid



A mixture of trans-ethyl 3-({4-[4-amino-3-(4-{[2-fluoro-4-trifluoromethylbenzoyl]amino}-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl}amino)propanoate (0.04 g, 0.06 mmol), p-dioxane (4 mL), potassium hydroxide (0.02 g, 0.31 mmol), a trace amount of methanol and water (0.4 mL) were heated at 80°C for 1 hour. The mixture was stirred at ambient temperature overnight and at 80°C for 4 hours. The solvents were evaporated and the residue was purified by preparative HPLC to yield trans-3-({4-[4-amino-3-(3-methoxy-4-{[2-methoxy-4-trifluoromethylbenzoyl]amino}phenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]cyclohexyl}amino)propanoic acid (0.04 g, 0.06 mmol) as a white solid: ^{1}H NMR (DMSO-d_6, 400MHz) δ 10.72 (s, 1H), 8.61(d, 1H), 8.28 (d, 1H), 8.24 (s, 1H), 7.61(s, 1H), 7.53 (d, 1H), 7.33 (s, 1H), 7.29 (d, 1H), 4.72 (m, 1H), 4.20 (s, 3H), 4.05 (s, 3H), 1.44-3.61 (m, 13H); RP-HPLC (Hitachi HPLC, Hypersil C18, 5μm, 100A,

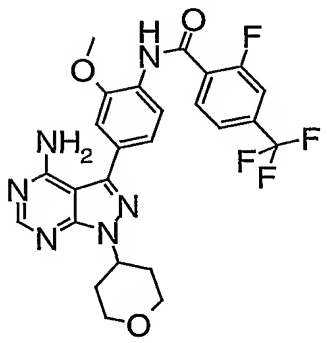
250x4.6mm; 25%-100% acetonitrile - 0.05M ammonium acetate over 10 min, 1mL/min) R_t 6.36 min. MS: MH^+ 628.

Example 877: *N*1-[4-(4-Amino-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-trifluoromethylbenzamide



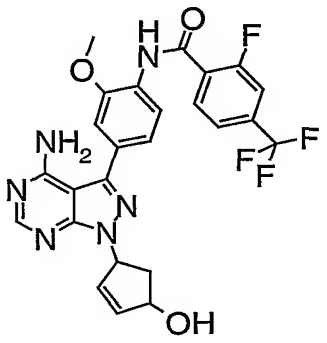
A mixture of *N*1-[4-(4-amino-1-trityl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-trifluoromethylbenzamide (2.10 g, 1.75 mmol), 6 N aqueous hydrochloric acid (10 mL), p-dioxane (10 mL) and ethanol (8 mL) was heated at 50°C for 6 hours. The mixture was filtered and the solid was washed with ethanol, dried in a vacuum oven over the weekend, and purified by flash column chromatography on silica to provide *N*1-[4-(4-amino-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-trifluoromethylbenzamide (0.35 g, 0.78 mmol). The filtrate was concentrated and purified by flash column chromatography on silica and preparative HPLC to provide the same product *N*1-[4-(4-amino-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-trifluoromethylbenzamide (0.67 g, 1.51 mmol) as a white solid: ^{1}H NMR (DMSO-d_6, 400MHz) δ 13.58 (s, 1H), 9.90 (dd, 1H), 8.30(d, 1H), 8.23 (s, 1H), 8.05 (t, 1H), 7.90 (d, 1H), 7.75 (d, 1H), 7.36 (s, 1H), 7.24 (d, 1H), 3.94 (s, 3H); MS: MH^+ 447.

Example 878: *N*1-[4-(4-Amino-1-tetrahydro-2*H*-4-pyranyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-trifluoromethylbenzamide



Diethyl azodicarboxylate (0.07 mL, 0.45 mmol) was added into a mixture of *N*1-[4-(4-amino-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-trifluoromethylbenzamide (0.10 g, 0.22 mmol), triphenylphosphine (0.12 g, 0.45 mmol) and tetrahydro-4*H*-pyran-4-ol (0.04 g, 0.34 mmol) in tetrahydrofuran (5 mL) and the mixture was stirred at ambient temperature overnight. Tetrahydro-4*H*-pyran-4-ol (0.01 g, 0.11 mmol), triphenylphosphine (0.04 g, 0.15 mmol) and diethyl azodicarboxylate (0.02 mL, 0.15 mmol) were added and the mixture was stirred at ambient temperature for 5 hours. The solvents were evaporated and the residue was purified by preparative HPLC to yield *N*1-[4-(4-amino-1-tetrahydro-2*H*-4-pyranyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-2-fluoro-4-trifluoromethylbenzamide (0.03 g, 0.06 mmol) as a white solid: ^{1}H NMR (DMSO-d_6, 400MHz) δ 9.91 (dd, 1H), 8.30(d, 1H), 8.25 (s, 1H), 8.00 (t, 1H), 7.89 (d, 1H), 7.75 (d, 1H), 7.34 (s, 1H), 7.31 (d, 1H), 6.90 (br, 2H), 4.95 (m, 1H), 4.02 (m, 2H), 3.95 (s, 3H), 3.56 (t, 2H), 2.22 (m, 2H), 1.89 (m, 2H); MS: MH^+ 531.

Example 879: *N*1-{4-[4-Amino-1-(4-hydroxy-2-cyclopentenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide



A. 4-(4-Amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-2-

cyclopenten-1-ol

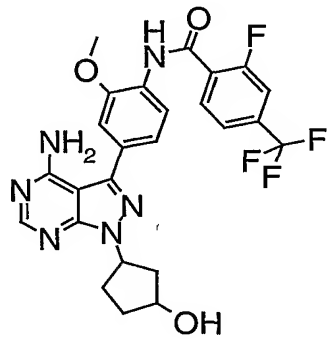
A mixture of tetrakis(triphenylphosphine)palladium(0) (0.04 g, 0.03 mmol), 3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.30 g, 1.14 mmol) and dimethyl sulfoxide (3 mL) was stirred at ambient temperature in the dark for 2 minutes and cooled to 0°C. A solution of 2,4*a*-dihydro-1*aH*-cyclopenta[*b*]oxirene (0.14 g, 1.72 mmol) in tetrahydrofuran (3 mL) was added into the mixture at 0°C and stirred at 0°C for 3 hours. The mixture was stirred at ambient temperature overnight and purified by preparative HPLC to yield 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-2-cyclopenten-1-ol (0.24 g, 0.70 mmol) as a white solid: RP-HPLC (Hitachi HPLC, Hypersil C18, 5μm, 100A, 250x4.6mm; 25%-100% acetonitrile - 0.05M ammonium acetate over 10 min, 1mL/min) R_t 4.23 min. MS: MH^+ 344.

B. *N*1-{4-[4-Amino-1-(4-hydroxy-2-cyclopentenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide

A mixture of 4-(4-amino-3-iodo-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-2-cyclopenten-1-ol (0.12 g, 0.35 mmol), *N*1-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-fluoro-4-trifluoromethylbenzamide (0.23 g, 0.53 mmol), tetrakis(triphenyl-phosphine)palladium(0) (0.02 g, 0.02 mmol) and sodium carbonate monohydrate (0.11 g, 0.88 mmol) was heated in a mixture of ethylene glycol dimethyl ether (6 mL) and water (3 mL) at 85° C for 6 hours under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature and solvents were removed under the reduced pressure. The residue was purified by preparative HPLC to yield *N*1-{4-[4-amino-1-(4-hydroxy-2-cyclopentenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide (0.18 g, 0.34 mmol) as a white solid: ^{1}H NMR (DMSO-d_6, 400MHz) δ 9.89 (dd, 1H), 8.31(d, 1H), 8.26 (s, 1H), 8.00 (t, 1H), 7.88 (d, 1H), 7.75 (d, 1H), 7.32 (s, 1H), 7.29 (d, 1H), 6.90 (br, 2H), 6.09 (d, 1H), 5.93 (d, 1H), 5.76 (m, 1H), 5.31 (m, 1H), 4.74 (m, 1H), 3.94 (s, 3H), 2.84 (m, 1H), 2.02 (m, 1H); RP-HPLC (Hitachi HPLC, Hypersil C18, 5μm, 100A, 250x4.6mm; 25%-100% acetonitrile - 0.05M ammonium acetate over 10 min, 1mL/min) R_t 8.50 min. MS:

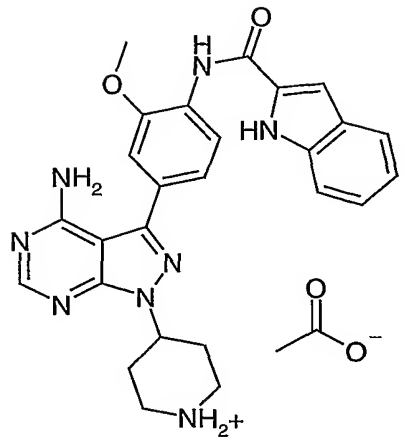
MH^+ 529.

Example 880: *N*1-{4-[4-Amino-1-(3-hydroxycyclopentyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide



A mixture of *N*1-{4-[4-amino-1-(4-hydroxy-2-cyclopentenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide (0.10 g, 0.19 mmol) and 10% palladium on carbon (0.03 g) in ethanol (10 mL) was stirred at ambient temperature under one atmosphere of hydrogen overnight. The mixture was filtered and the filtrate was purified by preparative HPLC to yield *N*1-{4-[4-amino-1-(3-hydroxycyclopentyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-2-fluoro-4-trifluoromethylbenzamide (0.07 g, 0.13 mmol) as a white sold: ^{1}H NMR (DMSO-d_6, 400MHz) δ 9.91 (dd, 1H), 8.31(d, 1H), 8.24 (s, 1H), 8.00 (t, 1H), 7.89 (d, 1H), 7.75 (d, 1H), 7.34 (s, 1H), 7.30 (d, 1H), 6.90 (br, 2H), 5.17 (m, 1H), 4.97 (m, 1H), 4.22 (m, 1H), 3.94 (s, 3H), 1.79-2.41 (m, 6H); MS: MH^+ 531.

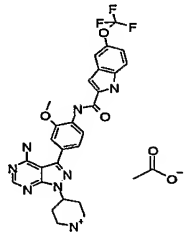
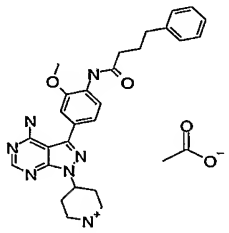
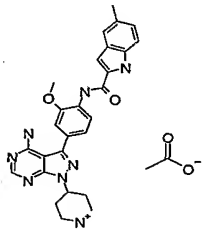
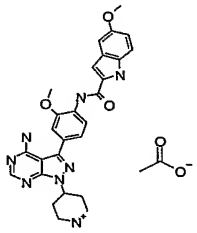
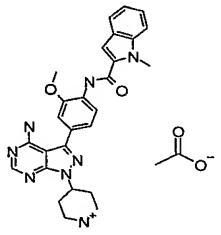
Example 881: 4-(4-Amino-3-{4-[(1*H*-2-indolylcarbonyl)amino]-3-methoxyphenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)hexahydropyridinium acetate

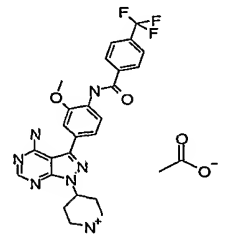
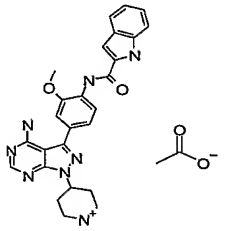
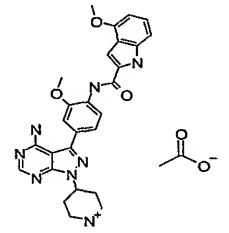
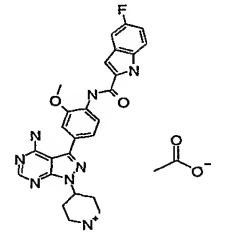
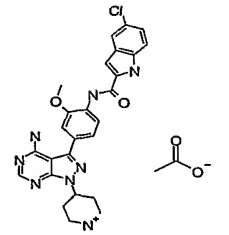
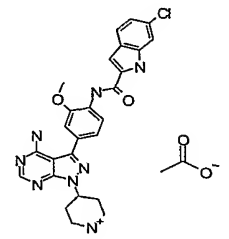


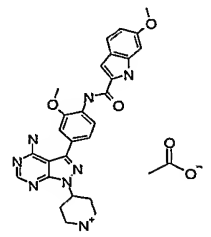
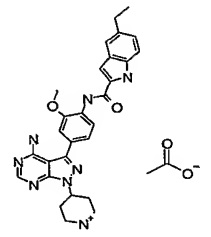
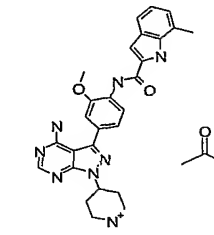
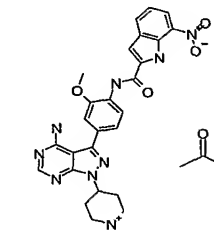
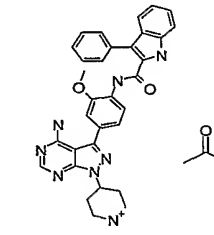
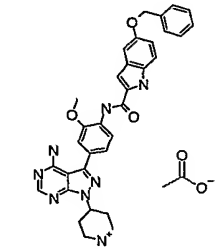
Oxalyl chloride (0.06 mL, 0.60 mmol) was added into a solution of indole-2-carboxylic acid (0.88 g, 0.546 mmol) in dichloromethane (5 mL) and tetrahydrofuran (5 mL) at 0°C. *N,N*-dimethylforamide (3 drops from 0.1 mL syringe) was added and the mixture was stirred at 0°C for 10 minutes and at ambient temperature for 20 minutes. The solvents and excess of reagents were evaporated under reduced pressure. The residue was taken into dichloromethane (2 mL) and the resulting solution (1.25 mL) was added into a solution of *tert*-butyl 4-[4-amino-3-(4-amino-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]-1-piperidinecarboxylate (0.12 g, 0.27 mmol) and pyridine (0.4 mL) in dichloromethane (1 mL). The mixture was stirred at ambient temperature for 2 hours. Trifluoroacetic acid (1 mL) was added and the mixture was stirred at ambient temperature for 2 hours. The solvents were evaporated under reduced pressure and the residue was purified by preparative HPLC to yield 4-(4-amino-3-{4-[(1*H*-2-indolylcarbonyl)amino]-3-methoxyphenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)hexahydropyridinium acetate (0.07 g, 0.14 mmol) as a white solid: ^{1}H NMR (DMSO-d_6, 400MHz) δ 11.85 (br, 1H), 9.45 (s, 1H), 8.24 (d, 1H), 8.12 (d, 1H), 7.68(d, 1H), 7.48 (d, 1H), 7.40 (s, 1H), 7.35 (s, 1H), 7.30 (d, 1H), 7.24 (t, 1H), 7.09 (t, 1H), 4.77 (m, 1H), 3.97 (s, 3H), 3.11 (m, 2H), 2.68 (m, 2H), 2.09 (m, 2H), 1.89 (s, 3H), 1.84 (m, 2H); MS: MH^+ 483.

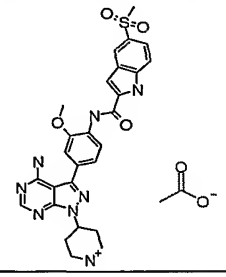
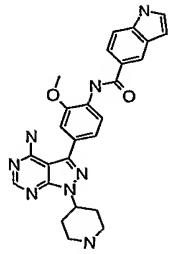
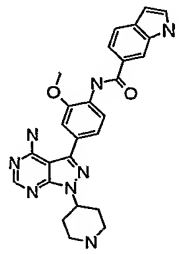
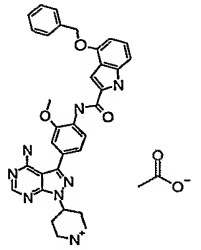
Example 882-902:

The same protocol as was used to prepare 4-(4-amino-3-{4-[(1*H*-2-indolylcarbonyl)amino]-3-methoxyphenyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)hexahydropyridinium acetate (Example 881) was used to prepare Examples 882-902.

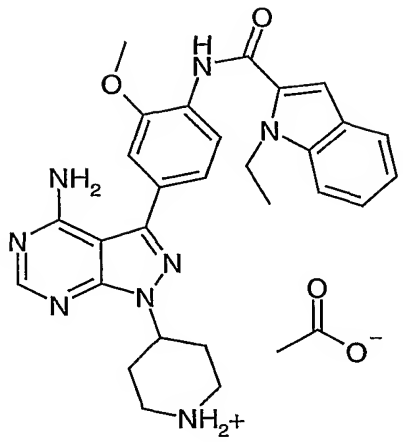
Structure	MS: MH+	HPLC Rt (min) (Hypersil C18, 5µm, 100A, 250x4.6mm; 25%-100% acetonitrile - 0.05M ammonium acetate over 10 min, 1mL/min)	Example No.
	567	6.97	882
	486	5.89	883
	497	6.28	884
	513	5.61	885
	497	6.39	886

	512	6.22	887
	483	5.73	888
	513	7.78	889
	501	8.23	890
	517	8.7	891
	517	8.73	892

	513	7.83	893
	511	9.07	894
	497	8.37	895
	528	7.9	896
	559	9.5	897
	589	7.45	898

	561	4.52	899
	483	6.35	900
	483	7.05	901
	589	6.63	902

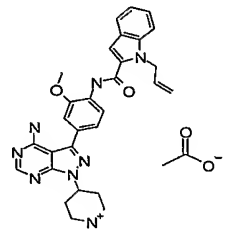
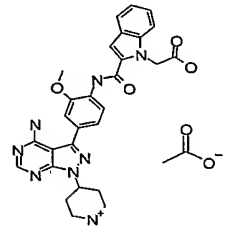
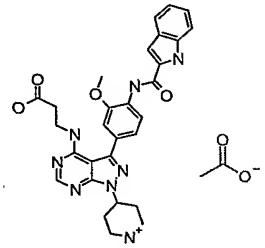
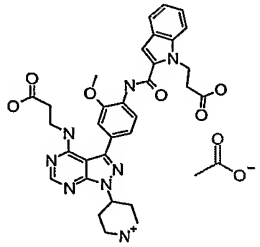
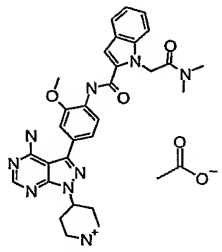
Example 903: 4-[4-Amino-3-(4-{[(1-ethyl-1*H*-2-indolyl)carbonyl]amino}-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]hexahydropyridinium acetate



Sodium hydride, 60% suspension in mineral oil (0.006 g, 0.15 mmol) was added into the solution of *N*2-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1*H*-2-indolecarboxamide (0.08 g, 0.14 mmol) in *N,N*-dimethylforamide (1.0 mL) at 0°C. The mixture was stirred at 0°C for 10 minutes and at ambient temperature for 20 minutes. A solution of ethyl iodide (0.02 g, 0.14 mmol) in *N,N*-dimethylforamide (0.5 mL) was added in and the mixture was stirred at ambient temperature overnight. Ethyl iodide (0.01 g, 0.07 mmol) was added in and the mixture was stirred at ambient temperature overnight. Trifluoroacetic acid (3 mL) was added and the mixture was stirred at ambient temperature for 24 hours. The solvents and excess reagents were evaporated under reduced pressure and the residue was purified by preparative HPLC to yield 4-[4-amino-3-(4-{[(1-ethyl-1*H*-2-indolyl)carbonyl]amino}-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]hexahydropyridinium acetate (0.05 g, 0.09 mmol) as a white solid: ^{1}H NMR (DMSO-d_6, 400MHz) δ 9.43 (s, 1H), 8.27 (s, 1H), 8.14 (d, 1H), 7.71(d, 1H), 7.61 (d, 1H), 7.34 (s, 2H), 7.31 (t, 2H), 7.15 (t, 1H), 4.96 (m, 1H), 4.62 (q, 2H), 3.96 (s, 3H), 3.00 (m, 2H), 2.28 (m, 2H), 2.03 (m, 2H), 1.91 (s, 3H), 1.33 (t, 3H); MS: MH^+ 511.

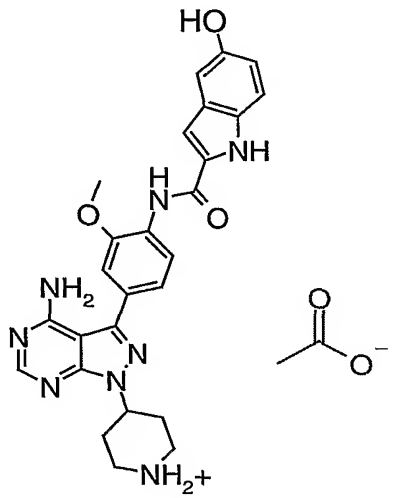
Example 904 to 908:

The same protocol that was used to prepare 4-[4-amino-3-(4-{[(1-ethyl-1*H*-2-indolyl)carbonyl]amino}-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]hexahydropyridinium acetate (Example 903) was used to prepare Examples 904-908.

Structure	MS: MH+	HPLC Rt (min) (Hypersil C18, 5µm, 100A, 250x4.6mm; 25%-100% acetonitrile - 0.05M ammonium acetate over 10 min, 1mL/min)	Example No.
	523	9.12	904
	540	6.03	905
	555	5.30	906
	627	6.55	907
	568	7.33	908

Example 909: *N*2-4-[4-Amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-

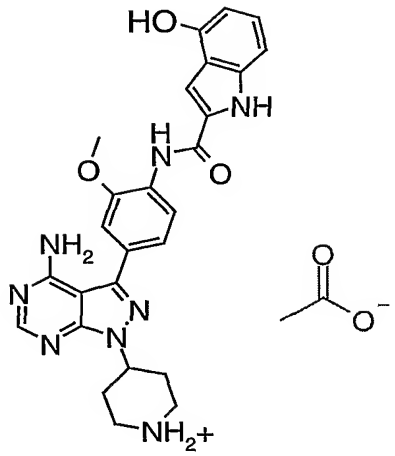
methoxyphenyl-5-hydroxy-1*H*-2-indolecarboxamide acetate salt



A mixture of *N*2-4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-5-(benzyloxy)-1*H*-2-indolecarboxamide (0.08 g, 0.14 mmol), 10% palladium on carbon (0.03 g) and trifluroacetic acid (a drop) in ethanol (12 mL) and tetrahydrofuran (12 mL) was hydrogenated under one atmosphere of hydrogen overnight. The mixture was filtered and the filtrate was purified by preparative HPLC to yield *N*2-4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-5-hydroxy-1*H*-2-indolecarboxamide acetate salt (0.02 g, 0.03 mmol) as a white solid:

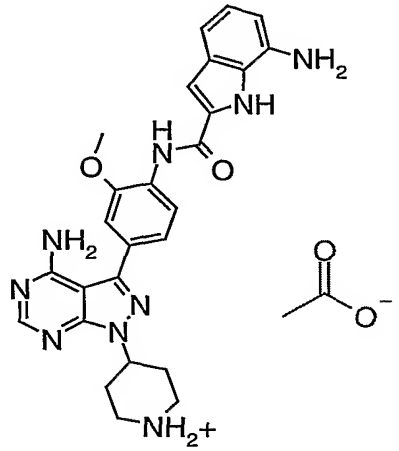
^{1}H NMR (DMSO-d_6, 400MHz) δ 11.55 (s, 1H), 9.29 (s, 1H), 8.88 (s, 1H), 8.28 (s, 1H), 8.18(d, 1H), 7.31 (m, 3H), 7.18 (s, 1H), 6.94 (s, 1H), 6.78 (dd, 1H), 5.06 (m, 1H), 3.97 (s, 3H), 3.44 (m, 2H), 3.17 (m, 2H), 2.39 (m, 2H), 2.11 (m, 2H), 1.91 (s, 3H); MS: MH^+ 499.

Example 910: *N*2-4-[4-Amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-4-hydroxy-1*H*-2-indolecarboxamide acetate salt



The same protocol that was used to prepare *N*2-4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-5-hydroxy-1*H*-2-indolecarboxamide acetate salt was used to prepare *N*2-4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-4-hydroxy-1*H*-2-indolecarboxamide acetate salt. RP-HPLC (Hitachi HPLC, Hypersil C18, 5μm, 100A, 250x4.6mm; 25%-100% acetonitrile - 0.05M ammonium acetate over 10 min, 1mL/min) R_t 4.60 min. MS: MH^+ 499.

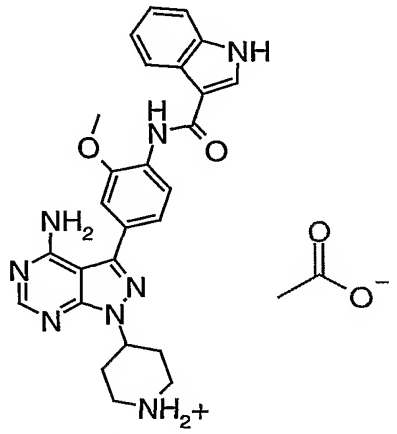
Example 911: *N*2-4-[4-Amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-7-amino-1*H*-2-indolecarboxamide acetate salt



Sodium dithionite (0.07 g, 0.41 mmol) was added into a hot solution of *N*2-4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-7-nitro-1*H*-2-indolecarboxamide acetate salt (0.04 g, 0.07 mmol) in water (2 mL) and ethanol (2 mL). The mixture was allowed to cool to ambient temperature. One drop

of concentrated hydrochloric acid was added and the mixture was purified by preparative HPLC to yield *N*2-4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-7-amino-1*H*-2-indolecarboxamide acetate salt (0.004 g, 0.01 mmol) as a white solid: RP-HPLC (Hitachi HPLC, Hypersil C18, 5µm, 100A, 250x4.6mm; 25%-100% acetonitrile - 0.05M ammonium acetate over 10 min, 1mL/min) R_t 6.60 min. MS: MH^+ 498.

Example 912: *N*3-4-[4-Amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-1*H*-3-indolecarboxamide acetate salt



A. *N*3-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1*H*-3-indolecarboxamide

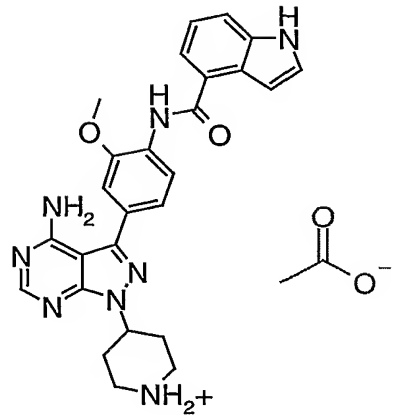
Oxalyl chloride (0.07 mL, 0.79 mmol) was added into a solution of indole-3-carboxylic acid (0.12 g, 0.72 mmol) in dichloromethane (4 mL) and tetrahydrofuran (3 mL) at 0°C. *N,N*-dimethylforamide (3 drops from 0.1 mL syringe) was added and the mixture was stirred at 0°C for 10 minutes and at ambient temperature for 20 minutes. The solvents and excess of reagents were evaporated under reduced pressure. The residue was taken into dichloromethane (2 mL) and the resulting solution (1.5 mL) was added into a solution of 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.09 g, 0.36 mmol) and pyridine (1 mL) in dichloromethane (2 mL). The mixture was stirred at ambient temperature overnight. The acid chloride solution in dichloromethane (0.3 mL) was added in and the mixture was stirred overnight. Water (a drop) was added in. The volatile components were evaporated under reduced pressure. The residue was partitioned between water and ethyl acetate. The aqueous layer was separated and extracted with ethyl acetate.

The organic extracts were combined and washed with saturated aqueous sodium chloride solution and dried over magnesium sulfate. The mixture was filtered and the solvent of the filtrate was evaporated to yield the crude which was purified by flash column chromatography on silica using n-heptane: ethyl acetate (2/1) as a mobile phase to yield *N*3-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1*H*-3-indolecarboxamide (0.11 g, 0.28 mmol) as a white solid: ^{1}H NMR ($CDCl_3$, 400MHz) δ 8.65 (m, 3H), 8.13 (d, 1H), 7.95 (s, 1H), 7.50 (m, 2H), 7.33(m, 3H), 4.02 (s, 3H), 1.36 (s, 12H); MS: MH^+ 393.

B. *N*3-4-[4-Amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-1*H*-3-indolecarboxamide acetate salt

A mixture of *N*3-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1*H*-3-indolecarboxamide (0.11 g, 0.28 mmol), 3-iodo-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine hydrochloric salt (0.10 g, 0.27 mmol), tetrakis(triphenyl-phosphine)palladium(0) (0.02 g, 0.02 mmol) and sodium carbonate monohydrate (0.13 g, 1.07 mmol) was heated in a mixture of ethylene glycol dimethyl ether (4 mL) and water (2 mL) at 85° C overnight under an atmosphere of nitrogen. The mixture was allowed to cool to ambient temperature and solvents were removed under the reduced pressure. The residue was purified by preparative HPLC to yield *N*3-4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-1*H*-3-indolecarboxamide acetate salt (0.09 g, 0.16 mmol) as a white solid: ^{1}H NMR (DMSO-d_6, 400MHz) δ 11.83 (br, 1H), 8.92 (s, 1H), 8.31 (m, 3H), 8.14 (dd, 1H), 7.50 (dd, 1H), 7.31 (m, 2H), 7.20 (m, 2H), 4.82 (m, 1H), 3.99 (s, 3H), 3.16 (m, 2H), 2.73 (m, 2H), 2.15 (m, 2H), 1.91 (s, 3H), 1.88 (m, 2H); MS: MH^+ 483.

Example 913: *N*4-4-[4-Amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-1*H*-4-indolecarboxamide acetate salt



The same protocol that prepare *N*3-4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-1*H*-3-indolecarboxamide acetate salt was used to *N*4-4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-1*H*-4-indolecarboxamide acetate salt. RP-HPLC (Hitachi HPLC, Hypersil C18, 5μm, 100A, 250x4.6mm; 25%-100% acetonitrile - 0.05M ammonium acetate over 10 min, 1mL/min) R_t 4.80 min. MS: MH^+ 483.

Example 914: *trans-N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide

A. 1-methyl-1*H*-2-indolecarbonyl chloride

A suspension of 1-methylindole-2-carboxylic acid (9.87 g, 56.4 mmol) in dichloro-methane (150 mL) was reacted with oxalyl chloride (8.58 g, 67.63 mmol). DMF was added (0.2 mL), upon which a vigorous reaction transpired. The mixture was stirred at ambient temperature for four hours. . The solvent was removed *in vacuo* to give 1-methyl-1*H*-2-indolecarbonyl chloride (10.69 g, 98%) as a light yellow solid.

^{1}H NMR ($CDCl_3$, 400MHz) δ7.70 (d, 1H), 7.66 (s, 1H), 7.44 (t, 1H), 7.35 (d, 1H), 7.18 (t, 1H), 3.98 (s, 3H).

B. *N*2-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-methyl-1*H*-2-indolecarboxamide

To a solution containing 1-methyl-1*H*-2-indolecarbonyl chloride (5.44 g, 0.0281 mol) and 2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (7.00 g, 0.0281 mol) in anhydrous dichloromethane (150 mL), *N*-ethyl-*N,N*-

diisopropylamine (4.9 mL, 0.0309 mol) was added dropwise at 0°C and the resulting solution was stirred at ambient temperature under an atmosphere of nitrogen for 18 hours. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between water (150 mL) and ethyl acetate (150 mL), The organic phase was washed with brine, dried with magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica using ethyl acetate/ n-heptane (1:6)) as mobile phase to yield *N*2-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-methyl-1*H*-2-indolecarboxamide (8.0 g, 0.0197 mol) as a white solid.

^{1}H NMR (DMSO-d_6, 400MHz) δ 9.35 (s, 1H), 8.03 (d, 1H), 7.69 (d, 1H), 7.57 (d, 1H), 7.33 (m, 3H), 7.29 (s, 1H), 7.14 (t, 1H), 4.02 (s, 3H), 3.91 (s, 3H), 1.31 (s, 12H).
TLC (ethyl acetate / heptane 1:3) R_f 0.44

C. *trans-N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide

A suspension of *trans*-3-iodo-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (0.100 g, 0.227 mmol) in ethylene glycol dimethyl ether (8 mL) was treated with *N*2-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-methyl-1*H*-2-indolecarboxamide (0.097g, 0.238 mmol), tetrakis(triphenylphosphine)palladium (0.016g, 0.014 mmol), and a solution of sodium carbonate (0.057g, 0.538 mmol) in water (4 mL). The reaction mixture was stirred for 21.5 h at 80°C. The precipitate was filtered, and the organic layer was evaporated under reduced pressure. Dichloromethane (15 mL) was added and the layers were partitioned. The aqueous layer was extracted with dichloromethane (200 mL). The combined organic layers were dried over magnesium sulfate, filtered, and evaporated under reduced pressure. The crude material was purified by flash chromatography on silica gel using a 10% methanol in dichloromethane to 50% methanol in dichloromethane step gradient on Sq 16x ISCO CombiFlash. The column afforded 0.083 g (68%) of *trans-N*2-(4-{4-amino-1-[4-(4-methylpiperazino)cyclohexyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide. ^{1}H NMR (d_6-DMSO)

δ 9.4316 (s, 1H), 8.2427 (s, 1H), 8.1207-8.1003 (d, 1H, *J* = 8.16 Hz), 7.7173-7.6974 (d, 1H, *J* = 7.96 Hz), 7.5979-7.5769 (d, 1H, *J* = 8.4 Hz), 7.3507-7.2758 (m, 4H), 7.1695-7.1321 (t, 1H), 4.6893-4.6324 (m, 1H), 4.0400 (s, 3H), 3.9571 (s, 3H), 2.5 (m, 3H), 2.4055-2.3279 (m, 5H), 2.1606 (s, 3H), 2.1094-1.9367 (m, 6H), 1.5214-1.4624 (m, 2H); LCMS (Thermoquest AQA single-quad MS, Genesis C18 column, 3μm particle size, 33 x 4.6mm; 70 % 50 mM ammonium Acetate in Water to 95% Acetonitrile over 6 min, 0.8 to 0.5 mL/min) R_t 2.12 min (100%), M^+ 594.3.

Example 915: *N*2-{4-[4-amino-1-(2-amino-4-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl-}1-methyl-1*H*-2-indolecarboxamide

Example 916: *N*2-(4-{4-amino-1-[2-(methylamino)-4-pyridyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide

Example 917: *N*2-(4-{4-amino-1-[2-(dimethylamino)-4-pyridyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide

Example 918: *N*2-(4-{4-amino-1-[2-(4-methylpiperazino)-4-pyridyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1*H*-2-indolecarboxamide

Example 919: *N*2-(4-{4-amino-1-[2-(4-methylpiperazino)-4-pyridyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1*H*-2-indolecarboxamide

Example 920: *N*2-{4-[4-amino-1-(2-morpholino-4-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide

Example 921: *N*2-[4-(4-amino-1-{2-[(2-hydroxyethyl)amino]-4-pyridyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-

indolecarboxamide

Example 922: *N*2-(4-{4-amino-1-[2-(aminomethyl)-4-pyridyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide

Example 923: *N*2-(4-{4-amino-1-[2-(aminocarbonyl)-4-pyridyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide

Example 924: 3-morpholino-1-(2-morpholino-4-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine

Example 925: *N*2-{4-[4-amino-1-(4-amino-2-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide

Example 926: *N*2-{4-[4-amino-1-(2-oxo-1,2-dihydro-4-pyridinyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide

Example 927: *N*2-{4-[4-amino-1-(4-morpholino-2-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide

Example 928: *N*2-(4-{4-amino-1-[4-(4-methylpiperazino)-2-pyridyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide

Example 929: *N*2-[4-(4-amino-1-{4-[(2-hydroxyethyl)amino]-2-pyridyl}-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1*H*-2-indolecarboxamide

Example 930: *N*2-{4-[4-amino-1-(6-amino-3-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-

3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide

Example 931: *N*2-{4-[4-amino-1-(6-morpholino-3-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1*H*-2-indolecarboxamide

Example 932: *N*2-(4-{4-amino-1-[6-(4-methylpiperazino)-3-pyridyl]-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1*H*-2-indolecarboxamide

Example 933: *Cis*-4-[4-(4-amino-3-{3-fluoro-4-[(5-methyl-1,3-benzoxazol-2-yl)amino]phenyl}-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl]-2-piperazinone

Example 934: *Trans*-4-[4-(4-amino-3-{3-fluoro-4-[(5-methyl-1,3-benzoxazol-2-yl)amino]phenyl}-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl]-2-piperazinone

Example 935: *Cis*-4-[4-(4-amino-3-{4-[(5-methyl-1,3-benzoxazol-2-yl)amino]phenyl}-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl]-2-piperazinone

Example 936: *Trans*-4-[4-(4-amino-3-{4-[(5-methyl-1,3-benzoxazol-2-yl)amino]phenyl}-1H-pyrazolo[3,4-d]pyrimidin-1-yl)cyclohexyl]-2-piperazinone

Example 937: R-N2-(4-{4-amino-1-[1-(1-methoxy-1-methylethyl)-3-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

Example 938: S-N2-(4-{4-amino-1-[1-(1-methoxy-1-methylethyl)-3-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

Example 939: R/S-N2-(4-{4-amino-1-[1-(1-methoxy-1-methylethyl)-3-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

Example 940: R-N2-(4-{4-amino-1-[1-(3-methoxypropyl)-3-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

Example 941: S-N2-(4-{4-amino-1-[1-(3-methoxypropyl)-3-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

Example 942: R/S-N2-(4-{4-amino-1-[1-(3-methoxypropyl)-3-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

Example 943: R-N2-(4-{4-amino-1-[1-(2-hydroxyethyl)-3-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

Example 944: S-N2-(4-{4-amino-1-[1-(2-hydroxyethyl)-3-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

Example 945: R/S-N2-(4-{4-amino-1-[1-(2-hydroxyethyl)-3-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

Example 946: R-N2-(4-{4-amino-1-[1-(2-{1,3-dihydroxypropyl})-3-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

Example 947: S-N2-(4-{4-amino-1-[1-(2-{1,3-dihydroxypropyl})-3-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

Example 948: R/S-N2-(4-{4-amino-1-[1-(2-{1,3-dihydroxypropyl})-3-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

Example 949: R-2-[3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidino]acetonitrile

Example 950: S-2-[3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidino]acetonitrile

Example 951: R/S-2-[3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidino]acetonitrile

Example 952: R-N2-(4-{4-amino-1-[1-(2-(methylsulfanyl)ethyl)-3-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

Example 953: S-N2-(4-{4-amino-1-[1-(2-(methylsulfanyl)ethyl)-3-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

Example 954: R/S-N2-(4-{4-amino-1-[1-(2-(methylsulfanyl)ethyl)-3-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

Example 955: R-N-methoxy-3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-

yl)amino]phenyl}-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-piperidinecarboximidamide

Example 956: S-N-methoxy-3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-piperidinecarboximidamide

Example 957: R/S-N-methoxy-3-(4-amino-3-{4-[(5,7-dimethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-1-piperidinecarboximidamide

Example 958: R-N2-(4-4-amino-1-[1-(1-2,2,2-trifluoroethyl)-3-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-ylphenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

Example 959: S-N2-(4-4-amino-1-[1-(1-2,2,2-trifluoroethyl)-3-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-ylphenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

Example 960: R/S-N2-(4-4-amino-1-[1-(1-2,2,2-trifluoroethyl)-3-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-ylphenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

Example 961: N2-{4-[4-amino-1-(1H-4-imidazolylmethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]phenyl}-5,7-dimethyl-1,3-benzoxazol-2-amine

Example 962: N2-(4-{4-amino-1-[1H-4-(2-methyl-imidazolyl)methyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

Example 963: N2-(4-{4-amino-1-[1H-4-(2-amino-imidazolyl)methyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

Example 964: N2-4-[4-amino-1-(1H-4-imidazolyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]phenyl-5,7-dimethyl-1,3-benzoxazol-2-amine

Example 965: N2-(4-{4-amino-1-[1H-4-(2-amino-imidazolyl)]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

Example 966: N2-(4-{4-amino-1-[1H-4-(2-methyl-imidazolyl)]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}phenyl)-5,7-dimethyl-1,3-benzoxazol-2-amine

Example 967: 1-(4-{4-amino-3-[4-(1,3-benzoxazol-2-ylamino)phenyl]-1H-pyrazolo[3,4-d]pyrimidin-1-yl}piperidino)-2-methyl-2-(methylamino)-1-propanone

Example 968: 1-[4-(4-amino-3-{4-[(5-methyl-1,3-benzoxazol-2-yl)amino]phenyl}-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidino]-2-methyl-2-(methylamino)-1-propanone

Example 969: 1-[4-(4-amino-3-{4-[(5-ethyl-1,3-benzoxazol-2-yl)amino]phenyl}-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidino]-2-methyl-2-(methylamino)-1-propanone

Example 970: 1-[4-(4-amino-3-{4-[(5-chloro-1,3-benzoxazol-2-yl)amino]phenyl}-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidino]-2-methyl-2-(methylamino)-1-propanone

Example 971: {4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}(1*H*-4-pyrazolyl)methanone

Example 972: 1-(4-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]benzoyl}-1*H*-1-pyrazolyl)-1-ethanone

Example 973: {4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-

yl]phenyl}(1-methyl-1*H*-4-pyrazolyl)methanone

Example 974: {4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}(1-benzyl-1*H*-4-pyrazolyl)methanone

Example 975: {4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}(1-benzoyl-1*H*-4-pyrazolyl)methanone

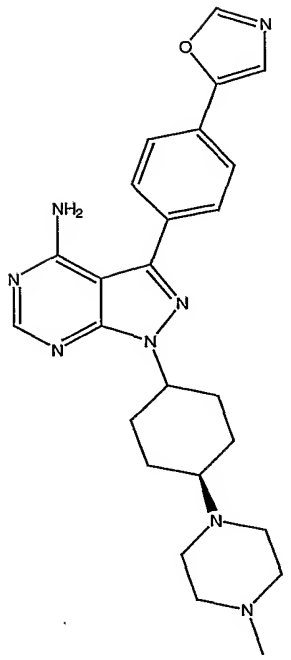
Example 976: {4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}(5-isoxazolyl)methanone

Example 977: {4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}(3-methyl-5-isoxazolyl)methanone

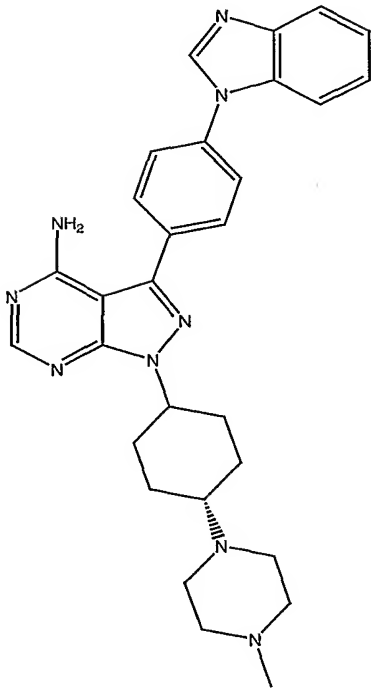
Example 978: {4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}(3-phenyl-5-isoxazolyl)methanone

Example 979: *N*5-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}-3-phenyl-5-isoxazolamine

Example 980: *N*5-{4-[4-amino-1-(4-piperidyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-yl]phenyl}-3-(trifluoromethyl)-5-isoxazolamine

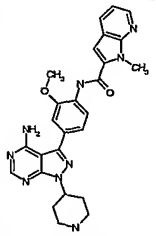
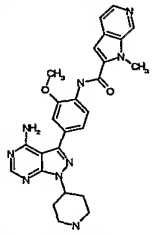
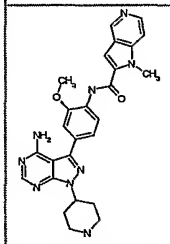
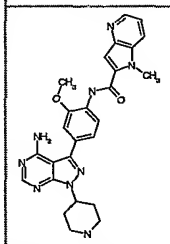
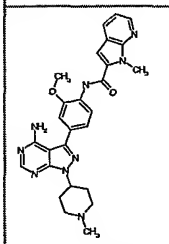
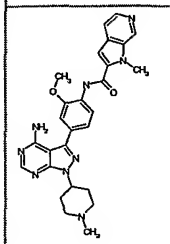


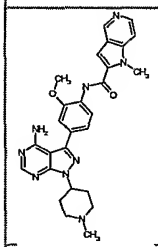
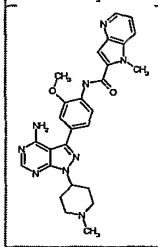
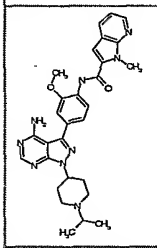
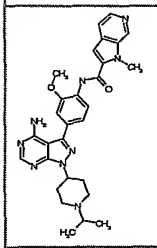
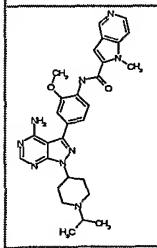
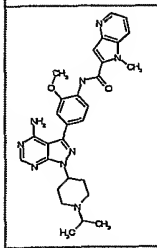
Example 981

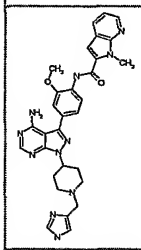
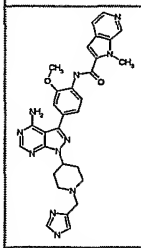
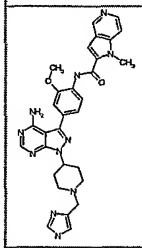
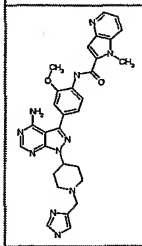
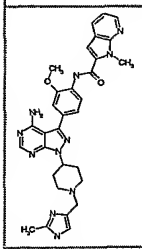
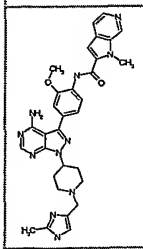


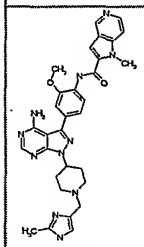
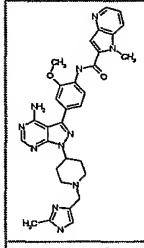
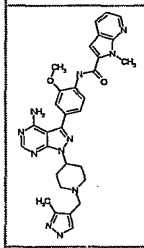
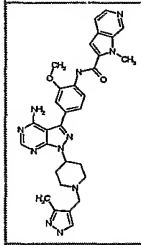
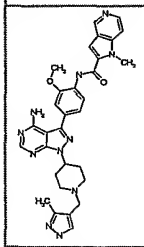
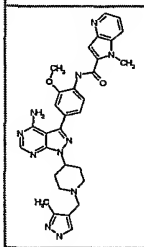
Example 982

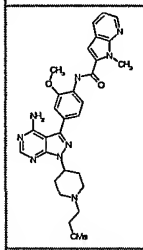
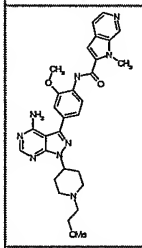
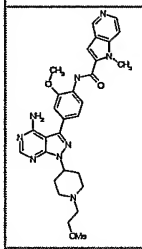
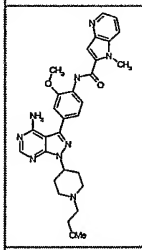
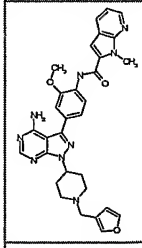
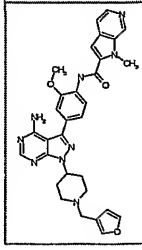
Other Examples include the following compounds:

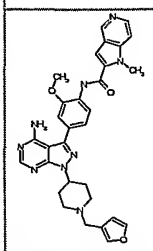
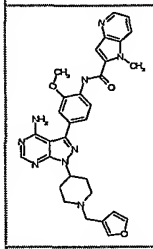
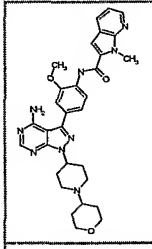
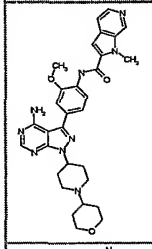
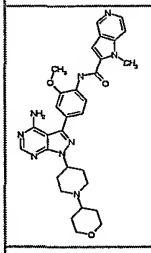
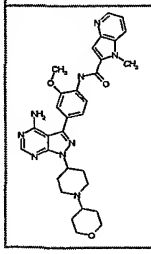
Structure	Name
	N2-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide
	N2-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide
	N2-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
	N2-{4-[4-amino-1-(4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1H-pyrrolo[3,2-b]pyridine-2-carboxamide
	N2-{4-[4-amino-1-(1-methyl-4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide
	N2-{4-[4-amino-1-(1-methyl-4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide

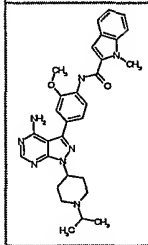
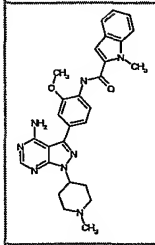
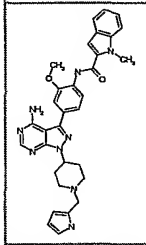
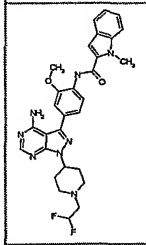
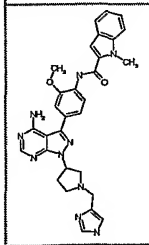
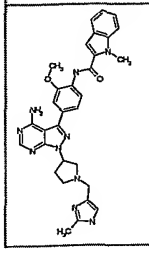
Structure	Name
	N2-{4-[4-amino-1-(1-methyl-4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
	N2-{4-[4-amino-1-(1-methyl-4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1H-pyrrolo[3,2-b]pyridine-2-carboxamide
	N2-{4-[4-amino-1-(1-isopropyl-4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide
	N2-{4-[4-amino-1-(1-isopropyl-4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide
	N2-{4-[4-amino-1-(1-isopropyl-4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
	N2-{4-[4-amino-1-(1-isopropyl-4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1H-pyrrolo[3,2-b]pyridine-2-carboxamide

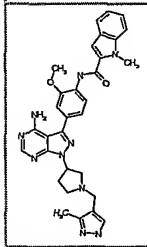
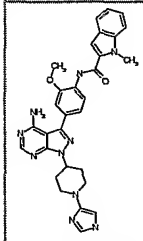
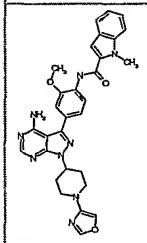
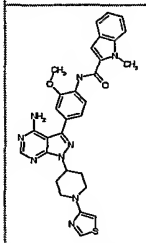
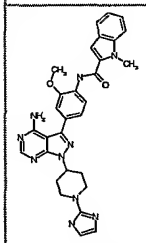
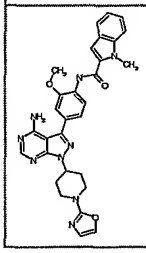
Structure	Name
	N2-(4-{4-amino-1-[1-(1H-4-imidazolylmethyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide
	N2-(4-{4-amino-1-[1-(1H-4-imidazolylmethyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide
	N2-(4-{4-amino-1-[1-(1H-4-imidazolylmethyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
	N2-(4-{4-amino-1-[1-(1H-4-imidazolylmethyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1H-pyrrolo[3,2-b]pyridine-2-carboxamide
	N2-[4-(4-amino-1-{1-[(2-methyl-1H-4-imidazolyl)methyl]-4-piperidyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide
	N2-[4-(4-amino-1-{1-[(2-methyl-1H-4-imidazolyl)methyl]-4-piperidyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide

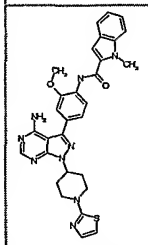
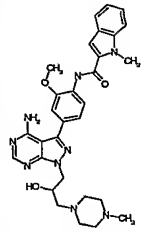
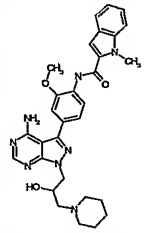
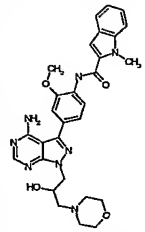
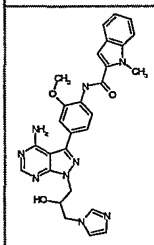
Structure	Name
	N2-[4-(4-amino-1-{1-[(2-methyl-1H-4-imidazolyl)methyl]-4-piperidyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
	N2-[4-(4-amino-1-{1-[(2-methyl-1H-4-imidazolyl)methyl]-4-piperidyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1H-pyrrolo[3,2-b]pyridine-2-carboxamide
	N2-[4-(4-amino-1-{1-[(3-methyl-1H-4-pyrazolyl)methyl]-4-piperidyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide
	N2-[4-(4-amino-1-{1-[(3-methyl-1H-4-pyrazolyl)methyl]-4-piperidyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide
	N2-[4-(4-amino-1-{1-[(3-methyl-1H-4-pyrazolyl)methyl]-4-piperidyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
	N2-[4-(4-amino-1-{1-[(3-methyl-1H-4-pyrazolyl)methyl]-4-piperidyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1H-pyrrolo[3,2-b]pyridine-2-carboxamide

Structure	Name
	N2-(4-{4-amino-1-[1-(2-methoxyethyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide
	N2-(4-{4-amino-1-[1-(2-methoxyethyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide
	N2-(4-{4-amino-1-[1-(2-methoxyethyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
	N2-(4-{4-amino-1-[1-(2-methoxyethyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1H-pyrrolo[3,2-b]pyridine-2-carboxamide
	N2-(4-{4-amino-1-[1-(3-furylmethyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide
	N2-(4-{4-amino-1-[1-(3-furylmethyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide

Structure	Name
	N2-(4-{4-amino-1-[1-(3-furylmethyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
	N2-(4-{4-amino-1-[1-(3-furylmethyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1H-pyrrolo[3,2-b]pyridine-2-carboxamide
	N2-{4-[4-amino-1-(1-tetrahydro-2H-4-pyranyl-4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1H-pyrrolo[2,3-b]pyridine-2-carboxamide
	N2-{4-[4-amino-1-(1-tetrahydro-2H-4-pyranyl-4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1H-pyrrolo[2,3-c]pyridine-2-carboxamide
	N2-{4-[4-amino-1-(1-tetrahydro-2H-4-pyranyl-4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1H-pyrrolo[3,2-c]pyridine-2-carboxamide
	N2-{4-[4-amino-1-(1-tetrahydro-2H-4-pyranyl-4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1H-pyrrolo[3,2-b]pyridine-2-carboxamide

Structure	Name
	N2-{4-[4-amino-1-(1-isopropyl-4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1H-2-indolecarboxamide
	N2-{4-[4-amino-1-(1-methyl-4-piperidyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1H-2-indolecarboxamide
	N2-(4-{4-amino-1-[1-(1H-2-pyrrolylmethyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1H-2-indolecarboxamide
	N2-(4-{4-amino-1-[1-(2,2-difluoroethyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1H-2-indolecarboxamide
	N2-(4-{4-amino-1-[1-(1H-4-imidazolylmethyl)tetrahydro-1H-3-pyrrolyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1H-2-indolecarboxamide
	N2-[4-(4-amino-1-{1-[(2-methyl-1H-4-imidazolyl)methyl]tetrahydro-1H-3-pyrrolyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1H-2-indolecarboxamide

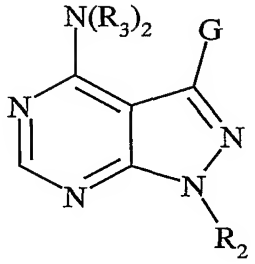
Structure	Name
	N2-[4-(4-amino-1-{1-[(3-methyl-1H-4-pyrazolyl)methyl]tetrahydro-1H-3-pyrrolyl}-1H-pyrazolo[3,4-d]pyrimidin-3-yl)-2-methoxyphenyl]-1-methyl-1H-2-indolecarboxamide
	N2-(4-{4-amino-1-[1-(1H-4-imidazolyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1H-2-indolecarboxamide
	N2-(4-{4-amino-1-[1-(1,3-oxazol-4-yl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1H-2-indolecarboxamide
	N2-(4-{4-amino-1-[1-(1,3-thiazol-4-yl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1H-2-indolecarboxamide
	N2-(4-{4-amino-1-[1-(1H-2-imidazolyl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1H-2-indolecarboxamide
	N2-(4-{4-amino-1-[1-(1,3-oxazol-2-yl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1H-2-indolecarboxamide

Structure	Name
	N2-(4-{4-amino-1-[1-(1,3-thiazol-2-yl)-4-piperidyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1H-2-indolecarboxamide
	N2-(4-{4-amino-1-[2-hydroxy-3-(4-methylpiperazino)propyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1H-2-indolecarboxamide
	N2-{4-[4-amino-1-(2-hydroxy-3-piperidinopropyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1H-2-indolecarboxamide
	N2-{4-[4-amino-1-(2-hydroxy-3-morpholinopropyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxyphenyl}-1-methyl-1H-2-indolecarboxamide
	N2-(4-{4-amino-1-[2-hydroxy-3-(1H-1-imidazolyl)propyl]-1H-pyrazolo[3,4-d]pyrimidin-3-yl}-2-methoxyphenyl)-1-methyl-1H-2-indolecarboxamide

CLAIMS

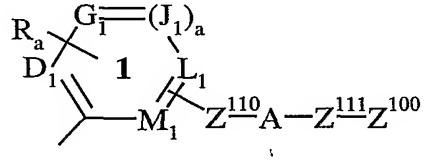
We claim:

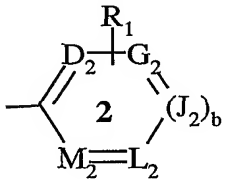
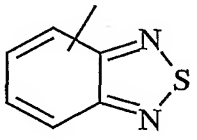
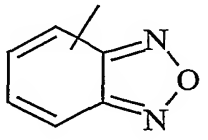
1. A compound of Formula (I)

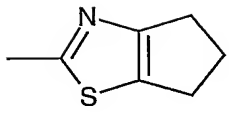


(I)

racemic-diastereomeric mixtures, optical isomers, pharmaceutically-acceptable salts, prodrugs or biologically active metabolites thereof wherein:

G is 

where Z^{100} is  or a group optionally substituted with R_1 selected from the group consisting of alkyl, cycloalkyl, pyrrolidinyl, quinolinyl, quinoxalinyl, quinazolinyl, isoquinolinyl, phthalazinyl, imidazo[1,2-a]pyrimidinyl, 1H-imidazo[1,2-a]imidazolyl, imidazo[2,1-b][1,3]thiazolyl, naphthyl, tetrahydronaphthyl, benzothienyl, furanyl, thienyl, benzoxazolyl, benzoisoxazolyl, benzothiazolyl,  ,  ,



, thiazolyl, benzofuranyl, 2,3-dihydrobenzofuranyl, indolyl, isoxazolyl, tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, pyrazolyl, pyrrolyl, pyrrolopyridinyl, H-pyridinone, oxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, indolinyl, indazolyl, imidazo[1,2-a]pyridinyl, benzoisothiazolyl, 1,1-dioxybenzoisothiazolyl, pyrido-oxazolyl, pyrido-thiazolyl, pyrimido-oxazolyl, pyrimido-thiazolyl and benzimidazolyl;

Z^{110} is a covalent bond, or an optionally substituted (C_1-C_6) which is optionally substituted with one or more substituents selected from the group consisting of alkyl, CN, OH, halogen, NO_2, COOH, substituted or unsubstituted amino and substituted or unsubstituted phenyl;

Z^{111} is a covalent bond, an optionally substituted (C_1-C_6) or an optionally substituted -$(CH_2)_n$-cycloalkyl-$(CH_2)_n$-; where the optionally substituted groups are optionally substituted with one or more substituents selected from the group consisting of alkyl, CN, OH, halogen, NO_2, COOH, substituted or unsubstituted amino and substituted or unsubstituted phenyl;

R_a and R_1 each represent one or more substituents for each occurrence independently selected from the group consisting of hydrogen, halogen, -CN, -NO_2, -C(O)OH, -C(O)H, -OH, -C(O)O-alkyl, -C(O)O-aryl, -C(O)O-heteroaryl, -C(O)-alkyl, -C(O)-aryl, -C(O)-heteroaryl, substituted or unsubstituted carboxamido, tetrazolyl, trifluoromethylcarbonylamino, trifluoromethylsulfonamido, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryloxy, substituted or unsubstituted heteroaryloxy, substituted or unsubstituted heteroarylalkoxy, substituted or unsubstituted arylalkoxy, substituted or unsubstituted alkyl-$S(O)_p$-, substituted or unsubstituted alkyl-S-, substituted or unsubstituted aryl-$S(O)_p$-,

substituted or unsubstituted heteroaryl-$S(O)_p$-, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted alkynyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted amido groups, substituted or unsubstituted heteroarylthio, substituted or unsubstituted arylthio, $-Z^{105}-C(O)N(R)_2$, $-Z^{105}-N(R)-C(O)-Z^{200}$, $-Z^{105}-N(R)-S(O)_2-Z^{200}$, $-Z^{105}-N(R)-C(O)-N(R)-Z^{200}$, R_c and CH_2OR_c;

where R_c for each occurrence is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, $-CH_2-NR_dR_e$, $-W-(CH_2)_t-NR_dR_e$, $-W-(CH_2)_t-O$-alkyl, $-W-(CH_2)_t-S$-alkyl, or $-W-(CH_2)_t-OH$;

Z^{105} for each occurrence is independently a covalent bond or (C_1-C_6);

Z^{200} for each occurrence is independently a substituted or unsubstituted (C_1-C_6), substituted or unsubstituted phenyl or substituted or unsubstituted -(C_1-C_6)-phenyl;

R_d and R_e for each occurrence are independently H, alkyl, alkanoyl or SO_2-alkyl; or R_d, R_e and the nitrogen atom to which they are attached together form a five- or six-membered heterocyclic ring;

t for each occurrence is independently an integer from 2 to 6;

W for each occurrence is independently a direct bond or O, S, S(O), $S(O)_2$, or NR_f, wherein R_f for each occurrence is independently H or alkyl; or

R_1 is a substituted or unsubstituted carbocyclic or heterocyclic ring fused with ring 2;

R_3 for each occurrence is, independently, hydrogen, hydroxy, substituted or unsubstituted alkyl, substituted or unsubstituted -C(O)-alkyl, a substituted or unsubstituted -C(O)-aryl, or a substituted or unsubstituted –C(O)-heteroaryl or substituted or unsubstituted alkoxy;

A is –(C_1-C_6) -, -O-; -S-; $-S(O)_p$-; -N(R)-; -N(C(O)OR)-; -N(C(O)R)-; $-N(SO_2R)$-; $-CH_2O$-; $-CH_2S$-; $-CH_2N(R)$-; -CH(NR)-; $-CH_2N(C(O)R)$)-; $-CH_2N(C(O)OR)$-; $-CH_2N(SO_2R)$-; -CH(NHR)-; -CH(NHC(O)R)-; $-CH(NHSO_2R)$-; -CH(NHC(O)OR)-; -CH(OC(O)R)-; -

CH(OC(O)NHR)-; -CH=CH-; -C(=NOR)-; -C(O)-; -CH(OR)-; -C(O)N(R)-; -N(R)C(O)-; -N(R)S(O)$_p$-; -OC(O)N(R)-; ; -N(R)-C(O)-(CH$_2$)$_n$-N(R)-, -N(R)C(O)O-; -N(R)-(CH$_2$)$_{n+1}$-C(O)-, -S(O)$_p$N(R)-; -O-(CR$_2$)$_{n+1}$-C(O)-, -O-(CR$_2$)$_{n+1}$-O-, -N(C(O)R)S(O)$_p$-; -N(R)S(O)$_p$N(R)-; -N(R)-C(O)-(CH$_2$)$_n$-O-, -C(O)N(R)C(O)-; -S(O)$_p$N(R)C(O)-; -OS(O)$_p$N(R)-; -N(R)S(O)$_p$O-; -N(R)S(O)$_p$C(O)-; -SO$_p$N(C(O)R)-; -N(R)SO$_p$N(R)-; -C(O)O-; -N(R)P(OR$_b$)O-; -N(R)P(OR$_b$)-; -N(R)P(O)(OR$_b$)O-; -N(R)P(O)(OR$_b$)-; -N(C(O)R)P(OR$_b$)O-; -N(C(O)R)P(OR$_b$)-; -N(C(O)R)P(O)(OR$_b$)O-, or -N(C(O)R)P(OR$_b$)-;

where R for each occurrence is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl or substituted or unsubstituted aryl;

R$_b$ for each occurrence is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl or substituted or unsubstituted aryl;

p is 1 or 2; or

in a phosphorus containing group, the nitrogen atom, the phosphorus atom, R and R$_b$ together form a five- or six-membered heterocyclic ring; or

A is NRSO$_2$ and R, R$_a$ and the nitrogen atom together form a substituted or unsubstituted five or-six-membered heterocyclic ring fused to ring 1; or

Z^{110}-A-Z^{111} taken together is a covalent bond; and

R$_2$ is H or a group of the formula -Z^{101}-Z^{102};

Z^{101} is a covalent bond, -(C$_1$-C$_6$)-, -(C$_1$-C$_6$)- -O-, -(C$_1$-C$_6$)- -C(O)-, -(C$_1$-C$_6$)- -C(O)O-, -(C$_1$-C$_6$)-C(O)-NH-, -(C$_1$-C$_6$)-C(O)-N((C$_1$-C$_6$))- or a substituted or unsubstituted phenyl group;

Z^{102} is hydrogen; a substituted or unsubstituted alkyl group; a substituted or unsubstituted cycloalkyl group; a substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted, saturated or unsaturated heterocyclic group; or a substituted or unsubstituted, saturated or unsaturated heterobicyclic group; wherein said substituted alkyl, substituted cycloalkyl, substituted cycloalkenyl, substituted heterocyclic and substituted heterobicyclic group having one or more

substituents each independently selected from the group consisting of hydroxyl, cyano, nitro, halo, substituted or unsubstituted (C_1-C_6), substituted or unsubstituted aryl, substituted or unsubstituted -C(O)-alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted -N(R)-(C_1-C_6) -OR, substituted or unsubstituted –N((C_1-C_6) -OR)$_2$,substituted or unsubstituted -N(R)-(C_1-C_6) -C(O)$_2$R, substituted or unsubstituted –(C_1-C_6) -N(R)-(C_1-C_6) -OR, substituted or unsubstituted –(C_1-C_6) -N(R)-(C_1-C_6) -N(R)$_2$, substituted or unsubstituted –(C_1-C_6) -C(O)N(R)-(C_1-C_6) -N(R)$_2$, substituted or unsubstituted sulfonamido, substituted or unsubstituted ureido, substituted or unsubstituted carboxamido, substituted or unsubstituted amino, substituted or unsubstituted –N(R)-(C_1-C_6) -OR, oxo, and a saturated, unsaturated or aromatic, substituted or unsubstituted heterocyclic group comprising one or more heteroatoms selected from the group consisting of N, O, and S; wherein the nitrogen atoms of said heterocyclic group or heterobicyclic group are independently optionally substituted by oxo, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted -C(O)N(R)$_2$, substituted or unsubstituted -C(O)-(C_1-C_6)-N(R)$_2$, -C(O)-alkyl, -C(O)-aryl, -C(O)-heteroaryl, substituted or unsubstituted arylalkyl group, or substituted or unsubstituted heteroarylalkyl; or

R_2 is a group of the formula -B-E, wherein B is a substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted azacycloalkyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkylsulfonyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aminoalkylcarbonyl, substituted or unsubstituted alkylene, substituted or unsubstituted aminoalkyl, substituted or unsubstituted alkylenecarbonyl or substituted or unsubstituted aminoalkylcarbonyl group; and E is substituted or unsubstituted alkyl, a substituted or unsubstituted cycloalkyl, substituted or unsubstituted azacycloalkyl, a

substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted (C_1-C_6)-azacycloalkyl-, substituted or unsubstituted azacycloalkylcarbonyl, substituted or unsubstituted azacycloalkylsulfonyl, substituted or unsubstituted azacycloalkylalkyl, substituted or unsubstituted heteroaryl-N(R)-(C_1-C_6)-, substituted or unsubstituted aryl-N(R)-(C_1-C_6)-, substituted or unsubstituted alkyl-N(R)-(C_1-C_6)-, substituted or unsubstituted heteroaryl-(C_1-C_6)-N(R)-, substituted or unsubstituted aryl-(C_1-C_6)-N(R)-, substituted or unsubstituted alkyl-(C_1-C_6)-N(R)-, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylcarbonyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted arylcarbonyl, substituted or unsubstituted heteroarylsulfonyl, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted arylsulfonyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted azacycloalkylcarbonylamino, substituted or unsubstituted heteroarylcarbonylamino, substituted or unsubstituted arylcarbonylamino, substituted or unsubstituted alkylcarbonylamino or substituted or unsubstituted aryl;

a is 1 and D_1, G_1, J_1, L_1 and M_1 are each independently selected from the group consisting of CR_a and N, provided that at least two of D_1, G_1, J_1, L_1 and M_1 are CR_a; or

a is 0, and one of D_1, G_1, L_1 and M_1 is NR_a, one of D_1, G_1, L_1 and M_1 is CR_a and the remainder are independently selected from the group consisting of CR_a and N, wherein R_a is as defined above;

b is 1 and D_2, G_2, J_2, L_2 and M_2 are each independently selected from the group consisting of CR_a and N, provided that at least two of D_2, G_2, J_2, L_2 and M_2 are CR_a; or

b is 0, and one of D_2, G_2, L_2 and M_2 is NR_a, one of D_2, G_2, L_2 and M_2 is CR_a and the remainder are independently selected from the group consisting of CR_a and N, wherein R_a is as defined above; and

n for each occurrence is independently an integer from 0 to 6;

provided that when A is –N(R)-, Z^{110} and Z^{111} are each a covalent bond, and

R_2 is a 3,4-dihydroxytetrahydrofur-2-yl or a 3,4-diacyloxytetrahydrofur-2-yl, then Z^{100} is not alkyl, tetrahydropyranyl, tetrahydrofuranyl, piperidinyl or pyrrolidinyl;

provided that when Z^{110} and Z^{111} are each a covalent bond, and R_2 is a 3,4-dihydroxytetrahydrofur-2-yl or a 3,4-diacyloxytetrahydrofur-2-yl, Z^{100} is a substituted or unsubstituted alkyl, then A is not alkyl, -O-, -C(O)-, -NHC(O)- or –C(O)O-;

provided that when Z^{110}-A-Z^{111} taken together are a covalent bond, then Z^{100} is not alkyl;

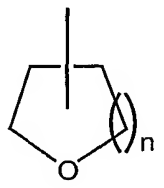
provided that when Z^{110}-A-Z^{111} taken together are a C_1-C_6 alkyl, then Z^{100} is not phenyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, furyl or thienyl; and

provided that when R_2 is a substituted or unsubstituted cyclopentyl, Z^{100} is an substituted or unsubstituted alkyl, Z^{110} and Z^{111} are each a covalent bond, then A is not –O-, -C(O)O-, or –N(R)-.

2. The compound of Claim 1 wherein R_3 is H; R_1 for each occurrence is independently selected from the group consisting of F, Cl, Br, I, CH_3, NO_2, OCF_3, OCH_3, CN, CO_2CH_3, CF_3, -$CH_2NR_dR_e$, t-butyl, pyridyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted benzyl, substituted or unsubstituted benzenesulfonyl, substituted or unsubstituted phenoxy, substituted or unsubstituted phenyl, substituted or unsubstituted amino, carboxyl, substituted or unsubstituted tetrazolyl, and substituted or unsubstituted styryl.

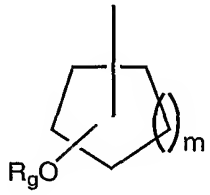
3. The compound of Claim 1 wherein R_3 is H; R_a for each occurrence is independently selected from the group consisting of F, Cl, Br, I, CH_3, NO_2, OCF_3, OCH_3, CN, CO_2CH_3, CF_3, t-butyl, pyridyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted benzyl, substituted or unsubstituted benzenesulfonyl, substituted or unsubstituted phenoxy, substituted or unsubstituted phenyl, substituted or unsubstituted amino, carboxyl, substituted or unsubstituted tetrazolyl, and substituted or unsubstituted styryl.

4. The compound of Claim 1 wherein R_3 is H; R_2 is of the formula



wherein n is 1, 2 or 3.

5. The compound of Claim 1 wherein R_3 is H; R_2 is of the formula



wherein:

m is 0, 1, 2 or 3;

R_g is H or $-(CH_2)_pN(R_4)R_5$;

p is an integer from 2 to 6;

R_4 and R_5 are each, independently, H, azabicycloalkyl or Y-Z;

Y is selected from the group consisting of $-C(O)-$, $-(CH_2)_q-$, $-S(O)_2-$, $-C(O)O-$, $-SO_2NH-$, $-CONH-$, $-(CH_2)_qO-$, $-(CH_2)_qNH-$, and $-(CH_2)_qS(O)_r-$;

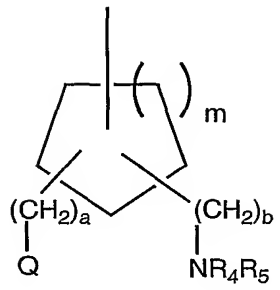
q is an integer from 0 to 6;

r is 0, 1 or 2; and

Z is a substituted or unsubstituted moiety selected from the group consisting of alkyl, alkoxy, amino, aryl, heteroaryl and heterocycloalkyl group; or

R_4, R_5 and the nitrogen atom to which they are attached together form a 3, 4, 5, 6 or 7-membered, substituted or unsubstituted heterocyclic or heterobicyclic group.

6. The compound of Claim 1 wherein R_3 is H; R_2 is of the formula



wherein:

m is 0, 1, 2 or 3;

a and b are each, independently, an integer from 0 to 6;

Q is $-OR_6$ or $-NR_4R_5$;

each R_4 and R_5 is, independently, H, azabicycloalkyl or Y-Z;

Y is selected from the group consisting of -C(O)-, $-(CH_2)_q-$, $-S(O)_2-$, -C(O)O-, $-SO_2NH-$, -CONH-, $(CH_2)_qO-$, $-(CH_2)_qNH-$, and $-(CH_2)_qS(O)_r-$;

q is an integer from 0 to 6;

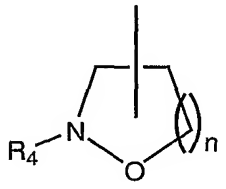
r is 0, 1 or 2; and

Z is a substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, amino, aryl, heteroaryl or heterocycloalkyl group; or

R_4, R_5 and the nitrogen atom to which they are attached together form a 3, 4, 5, 6 or 7-membered, substituted or unsubstituted heterocyclic or heterobicyclic group; and

R_6 is hydrogen or a substituted or unsubstituted alkyl group.

7. The compound of Claim 1 wherein R_3 is H; R_2 is of the formula



wherein:

n is 1, 2 or 3;

R_4 is H, azabicycloalkyl or Y-Z;

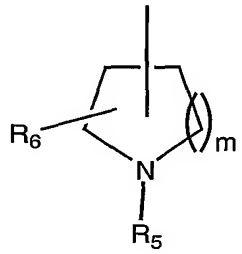
Y is selected from the group consisting of -C(O)-, $-(CH_2)_q-$, $-S(O)_2-$, -C(O)O-, $-SO_2NH-$, -CONH-, $(CH_2)_qO-$, $-(CH_2)_qNH-$, and $-(CH_2)_qS(O)_r-$;

q is an integer 0 to 6;

r is 0, 1 or 2; and

Z is a substituted or unsubstituted alkyl, substituted or unsubstituted amino, aryl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocycloalkyl group.

8. The compound of Claim 1 wherein R_3 is H; R_2 is of the formula



wherein;

m is 0, 1, 2 or 3;

R_5 is H, azabicycloalkyl or Y-Z;

Y is selected from the group consisting of a covalent bond, -C(O)-, -$(CH_2)_q$-, -$S(O)_2$-, -C(O)O-, -SO_2NH-, -CONH-, -$(CH_2)_qO$-, -$(CH_2)_qNH$-, -$(CH_2)_qC(O)$-, -$C(O)(CH_2)_q$- and -$(CH_2)_qS(O)_r$-, where the alkyl portion of -$(CH_2)_q$-, -$(CH_2)_qO$-, -$(CH_2)_qNH$-, -$(CH_2)_qC(O)$-, -$C(O)(CH_2)_q$- and -$(CH_2)_qS(O)_r$ is optionally substituted by a halogen, hydroxy or an alkyl group;

q is an integer from 0 to 6;

r is 0, 1 or 2; and

Z is a substituted or unsubstituted alkyl, substituted or unsubstituted amino, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocycloalkyl group; or

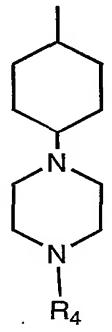
Y and Z together are a natural or unnatural amino acid, which may be mono- or di-alkylated at the amine nitrogen; and

R_6 represents one or more substituents each independently selected from the group consisting of hydrogen, hydroxy, oxo, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted

alkoxycarbonyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted aminocarbonyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted arylcarbonyl, substituted or unsubstituted heterocyclylcarbonyl, substituted or unsubstituted aminoalkyl and substituted or unsubstituted arylalkyl;

provided that the carbon atoms adjacent to the nitrogen atom are not substituted by a hydroxy group.

9. The compound of Claim 1 wherein R_3 is H; R_2 is of the formula



wherein:

R_4 is H, substituted or unsubstituted alkyl, substituted or unsubstituted azabicycloalkyl or Y-Z;

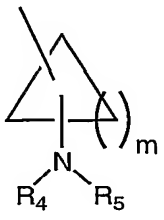
Y is selected from the group consisting of -C(O)-, $-(CH_2)_q-$,$-S(O)_2-$, -C(O)O-, $-SO_2NH-$, -CONH-, $-(CH_2)_qO-$, $-(CH_2)_qNH-$, and $-(CH_2)_qS(O)_r-$;

q is an integer from 0 to 6;

r is 0, 1 or 2; and

Z is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocycloalkyl.

10. The compound of Claim 1 wherein R_3 is H; R_2 is of the formula



wherein:

m is an integer from 1 to 6;

R_4 and R_5 are each, independently, H, substituted or unsubstituted azabicycloalkyl or Y-Z;

Y is selected from the group consisting of -C(O)-, $-(CH_2)_q-$, $-S(O)_2-$, -C(O)O-, $-SO_2NH-$, -CONH-, $-(CH_2)_qO-$, $-(CH_2)_qNH-$, and $-(CH_2)_qS(O)_r-$;

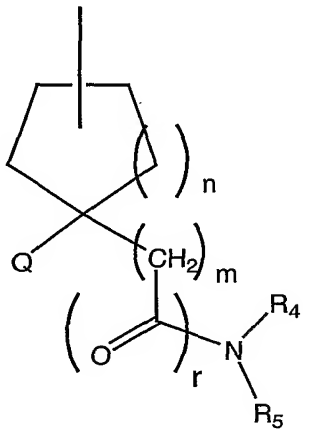
q is an integer from 0 to 6;

r is 0, 1 or 2; and

Z is a substituted or unsubstituted alkyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocycloalkyl group; or

R_4, R_5 and the nitrogen atom to which they are attached together form a 3, 4, 5, 6 or 7-membered, substituted or unsubstituted heterocyclic or substituted or unsubstituted heterobicyclic group.

11. The compound of Claim 1 wherein R_3 is H; R_2 is of the formula



wherein

n is an integer from 0 to 4;

r is 0 and m is an integer from 1 to 6; or

r is 1 and m is an integer from 0 to 6;

Q is $-OR_6$ or $-NR_4R_5$;

each R_4 and R_5 is, independently, H, substituted or unsubstituted azabicycloalkyl or Y-Z;

Y is selected from the group consisting of -C(O)-, $-(CH_2)_q-$, $-S(O)_2-$, -C(O)O-, $-SO_2NH-$, -CONH-, $-(CH_2)_qO-$, $-(CH_2)_qNH-$, and $-(CH_2)_qS(O)_r-$;

q is an integer from 0 to 6;

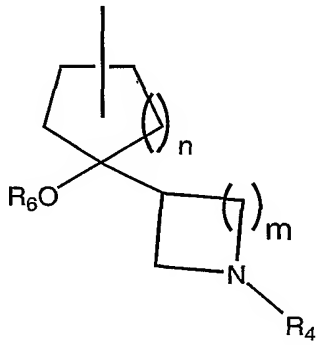
r is 0, 1 or 2; and

Z is a substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocycloalkyl group; or

R_4, R_5 and the nitrogen atom to which they are attached together form a 3, 4, 5 or 6-membered, substituted or unsubstituted heterocyclic group; and

R_6 is hydrogen or a substituted or unsubstituted alkyl group.

12. The compound of Claim 1 wherein R_3 is H; R_2 is of the formula



wherein:

n is an integer from 0 to 4;

m is an integer from 0 to 6;

R_4 is H, substituted or unsubstituted azabicycloalkyl or Y-Z;

Y is selected from the group consisting of -C(O)-, -$(CH_2)_q$-, -$S(O)_2$-, -C(O)O-, -SO_2NH-, -CONH-, -$(CH_2)_q$O-, -$(CH_2)_q$NH-, and-$(CH_2)_q$S(O)$_r$-;

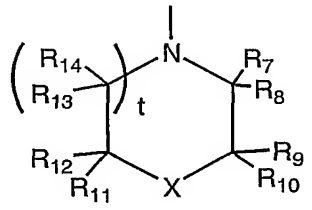
q is an integer from 0 to 6;

r is 0, 1 or 2;

Z is substituted or unsubstituted alkyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocycloalkyl; and

R_6 is hydrogen or a substituted or unsubstituted alkyl group.

13. The compound of Claim 10 wherein R_4, R_5 and the nitrogen atom together form a heterocyclic group of the formula



wherein:

R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13} and R_{14} are each, independently, lower alkyl or hydrogen; or

at least one pair of substituents R_7 and R_8; R_9 and R_{10}; R_{11} and R_{12}; or R_{13} and R_{14} together are an oxygen atom; or

at least one of R_7 and R_9 is cyano, $CONHR_{15}$, $COOR_{15}$, CH_2OR_{15} or $CH_2NR_{15}(R_{16})$, and

R_{15} and R_{16} are each, independently, H, azabicycloalkyl or V-L;

V is selected from the group consisting of -C(O)-, $-(CH_2)_p-$,$-S(O)_2-$, -C(O)O-, $-SO_2NH-$, -CONH-, $(CH_2)_qO-$, $-(CH_2)_qNH-$, and-$(CH_2)_qS(O)_r-$;

p is an integer from 0 to 6;

q is an integer from 0 to 6;

r is 0, 1 or 2;

L is substituted or unsubstituted alkyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocycloalkyl; or R_{15}, R_{16} and the nitrogen atom together form a 3, 4, 5, 6 or 7-membered, substituted or unsubstituted heterocyclic or a substituted or unsubstituted heterobicyclic group;

X is O, S, SO, SO_2, CH_2, $CHOR_{17}$ or NR_{17};

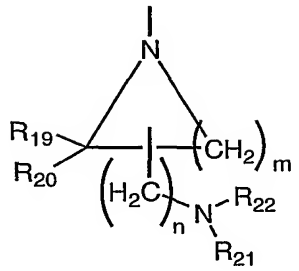
R_{17} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, $-C(NH)NH_2$, $-C(O)R_{17}$, or $-C(O)OR_{18}$;

R_{18} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl or substituted or unsubstituted arylalkyl; and

t is 0 or 1.

14. The compound of Claim 10 wherein R_4, R_5 and the nitrogen atom together

form a heterocycle of the formula



wherein:

R_{19} and R_{20} are each, independently, hydrogen or lower alkyl; or R_{19} and R_{20} together are an oxygen atom;

R_{21} and R_{22} are each, independently, H, substituted or unsubstituted azabicycloalkyl or V-L;

V is selected from the group consisting of -C(O)-, $-(CH_2)_p-$,$-S(O)_2-$, -C(O)O-, $-SO_2NH-$, -CONH-, $(CH_2)_qO-$, $-(CH_2)_qNH-$, and-$(CH_2)_qS(O)_r-$;

p is an integer from 0 to 6;

q is an integer from 0 to 6;

r is 0, 1 or 2; and

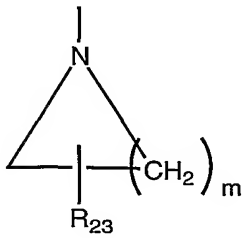
L is substituted or unsubstituted alkyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocycloalkyl group; or

R_{21}, R_{22} and the nitrogen atom together form a 3, 4, 5 or 6-membered, substituted or unsubstituted heterocyclic group; and

m is an integer from 1 to 6; and

n is an integer from 0 to 6.

15. The compound of Claim 10 wherein R_4, R_5 and the nitrogen atom together form a heterocyclic group of the formula



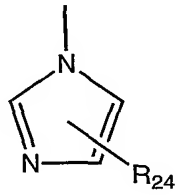
wherein:

m is an integer from 1 to 6;

R_{23} is CH_2OH, NRR', C(O)NRR' or COOR; and

R and R' are each, independently, hydrogen or substituted or unsubstituted alkyl, substituted or unsubstituted aryl or substituted or unsubstituted arylalkyl.

16. The compound of Claim 10 wherein R_4, R_5 and the nitrogen atom together form a heterocyclic group of the formula



wherein:

R_{24} is substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, carboxyl, cyano, $C(O)OR_{25}$, CH_2OR_{25}, $CH_2NR_{26}R_{27}$ or $C(O)NHR_{26}$;

R_{25} is substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocyclic or substituted or unsubstituted heterocycloaryl; and

R_{26} and R_{27} are each, independently, H, substituted or unsubstituted azabicycloalkyl or V-L;

V is selected from the group consisting of $-C(O)-$, $-(CH_2)_p-$,$-S(O)_2-$, $-C(O)O-$, $-SO_2NH-$, $-CONH-$, $(CH_2)_qO-$, $-(CH_2)_qNH-$, and-$(CH_2)_qS(O)_r-$;

p is an integer from 0 to 6;

q is an integer from 0 to 6;

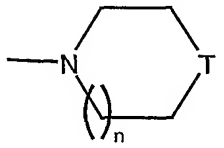
r is 0, 1 or 2; and

L is substituted or unsubstituted alkyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocycloalkyl; or

R_{26}, R_{27} and the nitrogen atom together form a 3, 4, 5 or 6-membered, substituted or unsubstituted heterocyclic group.

17. The compound of Claim 10 wherein at least one of R_4 and R_5 is of the

formula Y-Z, wherein Z is of the formula



wherein:

T is C(O), S, SO, SO_2, CHOR or NR;

R is hydrogen or a substituted or unsubstituted alkyl, substituted or unsubstituted aryl or substituted or unsubstituted arylalkyl group; and

n is 0, 1 or 2.

18. The compound of Claim 10 wherein:

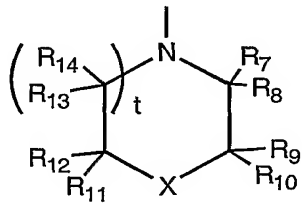
at least one of R_4 and R_5 is of the formula Y-Z;

Z is of the formula $-N(R_{28})R_{29}$; and

R_{28} and R_{29} are each, independently, substituted or unsubstituted carboxyalkyl, substituted or unsubstituted alkoxycarbonylalkyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted alkylcarbonyl or substituted or unsubstituted cyanoalkyl; or

R_{28} and R_{29}, together with the nitrogen atom, form a five- or six-membered substituted or unsubstituted heterocyclic group.

19. The compound of Claim 11 wherein R_4, R_5 and the nitrogen atom together form a heterocycle of the formula



wherein:

R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13} and R_{14} are each, independently, lower alkyl or

hydrogen; or

at least one pair of substituents R_7 and R_8; R_9 and R_{10}; R_{11} and R_{12}; or R_{13} and R_{14} together are an oxygen atom; or

at least one of R_7 and R_9 is cyano, $CONHR_{15}$, $COOR_{15}$, CH_2OR_{15} or $CH_2NR_{15}(R_{16})$; and

R_{15} and R_{16} are each, independently, H, substituted or unsubstituted azabicycloalkyl or V-L;

V is selected from the group consisting of -C(O)-, $-(CH_2)_p-$,$-S(O)_2-$, -C(O)O-, $-SO_2NH-$, -CONH-, $(CH_2)_qO-$, $-(CH_2)_qNH-$, and-$(CH_2)_qS(O)_r-$;

p is an integer from 0 to 6;

q is an integer from 0 to 6;

r is 0, 1 or 2; and

L is substituted or unsubstituted alkyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocycloalkyl; or

R_{15}, R_{16} and the nitrogen atom together form a 3, 4, 5, 6 or 7-membered, substituted or unsubstituted heterocyclic or heterobicyclic group; and

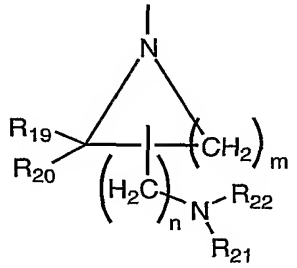
X is O, S, SO, SO_2, CH_2, $CHOR_{17}$ or NR_{17};

R_{17} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, $-C(NH)NH_2$, $-C(O)R_{18}$, or $-C(O)OR_{18}$;

R_{18} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl or substituted or unsubstituted arylalkyl; and

t is 0 or 1.

20. The compound of Claim 11 wherein R_4, R_5 and the nitrogen atom together form a heterocycle of the formula



wherein:

R_{19} and R_{20} are each, independently, hydrogen or lower alkyl; or

R_{19} and R_{20} together are an oxygen atom; and

R_{21} and R_{22} are each, independently, H, substituted or unsubstituted azabicycloalkyl or V-L;

V is selected from the group consisting of -C(O)-, $-(CH_2)_p-$,$-S(O)_2-$, -C(O)O-, $-SO_2NH-$, -CONH-, $(CH_2)_qO-$, $-(CH_2)_qNH-$, and-$(CH_2)_qS(O)_r-$;

p is an integer from 0 to 6;

q is an integer from 0 to 6;

r is 0, 1 or 2; and

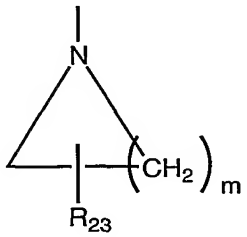
L is substituted or unsubstituted alkyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocycloalkyl group; or

R_{21}, R_{22} and the nitrogen atom together form a 3, 4, 5 or 6-membered, substituted or unsubstituted heterocyclic group; and

m is an integer from 1 to 6; and

n is an integer from 0 to 6.

21. The compound of Claim 11 wherein R_4, R_5 and the nitrogen atom together form a heterocyclic group of the formula



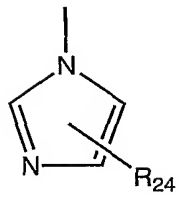
wherein:

m is an integer from 1 to 6; and

R_{23} is CH_2OH, NRR', C(O)NRR' or COOR;

R is hydrogen or a substituted or unsubstituted alkyl, substituted or unsubstituted aryl or substituted or unsubstituted arylalkyl group.

22. The compound of Claim 11 wherein R_4, R_5 and the nitrogen atom together form a heterocyclic group of the formula



wherein:

R_{24} is substituted or unsubstituted alkyl, substituted or unsubstituted aryl or substituted or unsubstituted arylalkyl , carboxyl, cyano, $C(O)OR_{25}$, CH_2OR_{25}, $CH_2NR_{26}R_{27}$ or $C(O)NHR_{26}$;

R_{25} is substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocyclic or substituted or unsubstituted heterocycloaryl group;

R_{26} and R_{27} are each, independently, H, substituted or unsubstituted azabicycloalkyl or V-L;

V is selected from the group consisting of -C(O)-, $-(CH_2)_p-$,$-S(O)_2-$, -C(O)O-, $-SO_2NH-$, -CONH-, $(CH_2)_qO-$, $-(CH_2)_qNH-$, and-$(CH_2)_qS(O)_r-$;

p is an integer from 0 to 6;

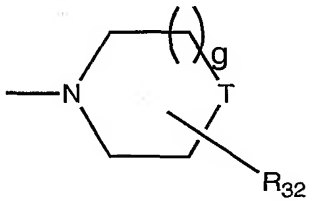
q is an integer from 0 to 6;

r is 0, 1 or 2; and

L is substituted or unsubstituted alkyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocycloalkyl group; or

R_{26}, R_{27} and the nitrogen atom together form a 3, 4, 5 or 6-membered, substituted or unsubstituted heterocyclic group.

23. The compound of Claim 11 wherein at least one of R_4 and R_5 is of the formula Y-Z, wherein Z is of the formula



wherein:

g is 0 or 1;

T is C(O), O, S, SO, SO_2, CH_2, $CHOR_{17}$ or NR_{17};

R_{17} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, $-C(NH)NH_2$, $-C(O)R_{18}$, or $-C(O)OR_{18}$;

R_{18} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl or substituted or unsubstituted arylalkyl; and

R_{32} is hydrogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxycarbonyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted aminocarbonyl, substituted or unsubstituted alkylcarbonyl or substituted or unsubstituted arylalkyl.

24. The compound of Claim 11 wherein;

at least one of R_4 and R_5 is of the formula Y-Z;

Z is of the formula $-N(R_{28})R_{29}$; and

R_{28} and R_{29} are each, independently, substituted or unsubstituted carboxyalkyl, substituted or unsubstituted alkoxycarbonylalkyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted alkylcarbonyl or substituted or unsubstituted cyanoalkyl; or

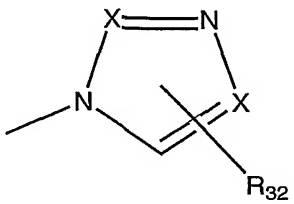
R_{28} and R_{29}, together with the nitrogen atom, form a five- or six-membered substituted or unsubstituted heterocyclic group.

25. The compound of Claim 8 wherein:

R_5 is Y-Z, wherein Z is of the formula $N(R_{30})R_{31}$; and

R_{30} and R_{31} are each, independently, hydrogen, alkyl, alkoxycarbonyl, alkoxyalkyl, hydroxyalkyl, aminocarbonyl, cyano, alkylcarbonyl or arylalkyl.

26. The compound of Claim 8 wherein R_5 is Y-Z, wherein Z is of the formula

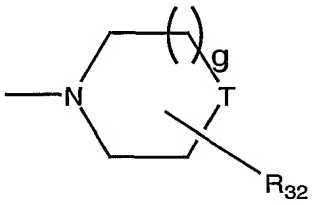


wherein:

each X is, independently, CH or N; and

R_{32} is hydrogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxycarbonyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted aminocarbonyl, substituted or unsubstituted alkylcarbonyl or substituted or unsubstituted arylalkyl group.

27. The compound of Claim 8 wherein R_5 is Y-Z, wherein Z is of the formula



wherein:

g is 0 or 1;

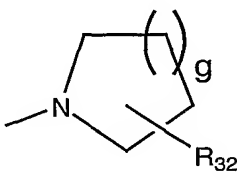
T is O, S, SO, SO_2, CH_2, $CHOR_{17}$ or NR_{17};

R_{17} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, $C(O)NH_2$, -$C(NH)NH_2$, -$C(O)R_{17}$, or -$C(O)OR_{18}$;

R_{18} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl or substituted or unsubstituted arylalkyl; and

R_{32} is hydrogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxycarbonyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted aminocarbonyl, substituted or unsubstituted alkylcarbonyl or substituted or unsubstituted arylalkyl group.

28. The compound of Claim 8 wherein R_5 is Y-Z, wherein Z is of the formula

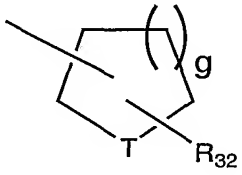


wherein:

g is 0, 1 or 2; and

R_{32} is hydrogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxycarbonyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted aminocarbonyl, substituted or unsubstituted alkylcarbonyl or substituted or unsubstituted arylalkyl group.

29. The compound of Claim 8 wherein R_5 is Y-Z, wherein Z is of the formula



wherein

T is C(O), O, S, SO, SO_2, CH_2, $CHOR_{17}$ or NR_{17};

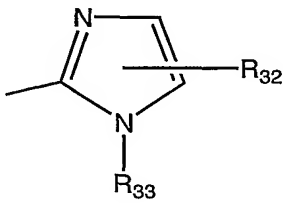
R_{17} is hydrogen, substituted or unsubstituted alkyl, aryl, arylalkyl, -$C(NH)NH_2$, -$C(O)R_{18}$, or -$C(O)OR_{18}$;

R_{18} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl or substituted or unsubstituted arylalkyl;

g is 0 or 1; and

R_{32} is hydrogen, cyano, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxycarbonyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted aminocarbonyl, substituted or unsubstituted alkylcarbonyl or substituted or unsubstituted arylalkyl group.

30. The compound of Claim 8 wherein R_5 is Y-Z, wherein Z is of the formula



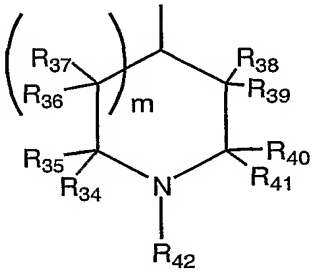
wherein:

R_{32} is hydrogen, cyano, substituted or unsubstituted alkyl, substituted or

unsubstituted alkoxycarbonyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted hydroxyalkyl, substituted or unsubstituted aminocarbonyl, alkylcarbonyl , substituted or unsubstituted thioalkoxy or substituted or unsubstituted arylalkyl; and

R_{33} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxycarbonyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted aminocarbonyl, perhaloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkylcarbonyl or substituted or unsubstituted arylalkyl.

31. The compound of Claim 1 wherein R_3 is H; R_2 is of the formula



wherein:

m is 0 or 1; and

R_{34}, R_{35}, R_{36}, R_{37}, R_{38}, R_{39}, R_{40} and R_{41} are each, independently, methyl or hydrogen; or

at least one pair of substituents R_{34} and R_{35}; R_{36} and R_{37}; R_{38} and R_{39}; or R_{40} and R_{41} together are an oxygen atom; and

R_{42} is H, substituted or unsubstituted azabicycloalkyl or Y-Z;

Y is selected from the group consisting of -C(O)-, $-(CH_2)_p-$,$-S(O)_2-$, -C(O)O-, $-SO_2NH-$, -CONH-, $(CH_2)_qO-$, $-(CH_2)_qNH-$, and-$(CH_2)_qS(O)_r-$;

p is an integer from 0 to 6;

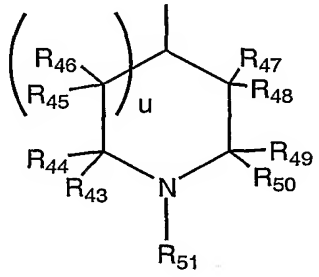
q is an integer from 0 to 6;

r is 0, 1 or 2; and

Z is substituted or unsubstituted alkyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted

heteroaryl or substituted or unsubstituted heterocycloalkyl group; or

R_{42} is of the formula



wherein:

u is 0 or 1;

R_{43}, R_{44}, R_{45}, R_{46}, R_{47}, R_{48}, R_{49} and R_{50} are each, independently, methyl or hydrogen; or

at least one pair of substituents R_{43} and R_{44}; R_{45} and R_{46}; R_{47} and R_{48}; or R_{49} and R_{50} together are an oxygen atom; and

R_{51} is H, substituted or unsubstituted azabicycloalkyl or V-L;

V is selected from the group consisting of -C(O)-, $-(CH_2)_p-$,$-S(O)_2-$, -C(O)O-, $-SO_2NH-$, -CONH-, $(CH_2)_qO-$, $-(CH_2)_qNH-$, and-$(CH_2)_qS(O)_r-$;

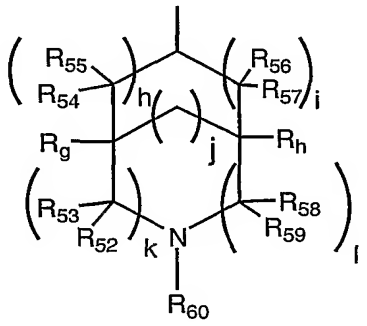
p is an integer from 0 to 6;

q is an integer from 0 to 6;

r is 0, 1 or 2; and

L is substituted or unsubstituted alkyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocycloalkyl.

32. The compound of Claim 1 wherein R_3 is H; R_2 is of the formula



wherein:

h, i, j, k and l are independently 0 or 1;

R_{52}, R_{53}, R_{54}, R_{55}, R_{56}, R_{57}, R_{58}, R_{59}, R_g and R_h are each, independently, methyl or hydrogen; or

at least one pair of substituents R_{52} and R_{53}; R_{54} and R_{55}; R_{56} and R_{57}; or R_{58} and R_{59} together are an oxygen atom; and

R_{60} is H, substituted or unsubstituted azabicycloalkyl or Y-Z;

Y is selected from the group consisting of -C(O)-, $-(CH_2)_p-$,$-S(O)_2-$, -C(O)O-, $-SO_2NH-$, -CONH-, $-(CH_2)_qO-$, $-(CH_2)_qNH-$, and $-(CH_2)_qS(O)_r-$;

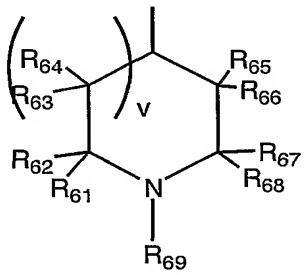
p is an integer from 0 to 6;

q is an integer from 0 to 6;

r is 0, 1 or 2; and

Z is substituted or unsubstituted alkyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocycloalkyl; or

R_{60} is of the formula



wherein:

v is 0 or 1;

R_{61}, R_{62}, R_{63}, R_{64}, R_{65}, R_{66}, R_{67} and R_{68} are each, independently, lower alkyl or hydrogen; or

at least one pair of substituents R_{61} and R_{62}; R_{63} and R_{64}; R_{65} and R_{66}; and R_{67} and R_{68} together are an oxygen atom; and

R_{69} is H, substituted or unsubstituted azabicycloalkyl or V-l;

V is selected from the group consisting of -C(O)-, $-(CH_2)_p-$,$-S(O)_2-$, -C(O)O-, $-SO_2NH-$, -CONH-, $(CH_2)_qO-$, $-(CH_2)_qNH-$, and-$(CH_2)_qS(O)_r-$;

p is an integer from 0 to 6;

q is an integer from 0 to 6;

r is 0, 1 or 2; and

L is substituted or unsubstituted alkyl, substituted or unsubstituted amino,

substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heterocycloalkyl.

33. A method of inhibiting one or more protein kinase activity in a patient comprising administering a therapeutically effective amount of a compound of Claim 1 or a physiologically acceptable salt, prodrug or biologically active metabolites thereof to said patient.

34. The method of Claim 33 wherein said protein kinase is selected from the group consisting of KDR, FGFR-1, PDGFRβ, PDGFRα, IGF-1R, c-Met, Flt-1, Flt-4, TIE-2, TIE-1, Lck, Src, fyn, Lyn, Blk, hck, fgr and yes.

35. A method of affecting hyperproliferative disorders in a patient comprising administering a therapeutically effective amount of a compound of Claim 1 or a physiologically acceptable salt, prodrug or biologically active metabolites thereof to said patient.

36. A method of affecting angiogenesis in a patient comprising administering a therapeutically effective amount of a compound of Claim 1 or a physiologically acceptable salt, prodrug or biologically active metabolites thereof to said patient.

37. The method of Claim 33 wherein the protein kinase is a protein serine/threonine kinase or a protein tyrosine kinase.

38. A method of treating one or more ulcers in a patient comprising administering a therapeutically effective amount of a compound of Claim 1 or a physiologically acceptable salt, prodrug or biologically active metabolites thereof to said patient.

39. The method of Claim 38 wherein the ulcer or ulcers are caused by a bacterial or fungal infection; or the ulcer or ulcers are Mooren ulcers; or the ulcer or ulcers are a symptom of ulcerative colitis.

40. A method of treating a condition in a patient comprising administering a therapeutically effective amount of a compound of Claim 1 or a physiologically acceptable salt, prodrug or biologically active metabolites thereof to said patient, wherein said condition is an ocular condition, a cardiovascular condition, a cancer, Crow-Fukase (POEMS) syndrome, a diabetic condition, sickle cell anaemia, chronic inflammation, systemic lupus, glomerulonephritis, synovitis, inflammatory bowel disease, Crohn's disease, glomerulonephritis, rheumatoid arthritis, osteoarthritis, multiple sclerosis, graft rejection, Lyme disease, sepsis, von Hippel Lindau disease, pemphigoid, psoriasis, Paget's disease, polycystic kidney disease, fibrosis, sarcoidosis, cirrhosis, thyroiditis, hyperviscosity syndrome, Osler-Weber-Rendu disease, chronic occlusive pulmonary disease, asthma or edema following burns, trauma, radiation, stroke, hypoxia, ischemia, ovarian hyperstimulation syndrome, preeclampsia, menometrorrhagia, endometriosis, or infection by Herpes simplex, Herpes Zoster, human immunodeficiency virus, parapoxvirus, protozoa or toxoplasmosis.

41. The method of Claim 40 wherein the ocular condition is ocular or macular edema, ocular neovascular disease, scleritis, radial keratotomy, uveitis, vitritis, myopia, optic pits, chronic retinal detachment, post-laser treatment complications, conjunctivitis, Stargardt's disease, Eales disease, retinopathy or macular degeneration.

42. The method of Claim 40 wherein the cardiovascular condition is atherosclerosis, restenosis, ischemia/reperfusion injury, vascular occlusion or carotid obstructive disease.

43. The method of Claim 40 wherein the cancer is a solid tumor, a sarcoma, fibrosarcoma, osteoma, melanoma, retinoblastoma, a rhabdomyosarcoma, glioblastoma, neuroblastoma, teratocarcinoma, an hematopoietic malignancy, Kaposi's sarcoma, Hodgkin's disease, lymphoma, myeloma, leukemia or malignant ascites.

44. The method of Claim 40 wherein the diabetic condition is insulin-dependent diabetes mellitus glaucoma, diabetic retinopathy or microangiopathy.

45. A method of decreasing fertility in a patient, said method comprising the step of administering to the patient an effective amount of a compound of Claim 1 or a physiologically acceptable salt, prodrug or biologically active metabolite thereof.

46. The method of Claim 36 wherein the compound or a physiologically acceptable salt, prodrug or biologically active metabolite thereof is administered in an amount effective to promote angiogenesis or vasculogenesis.

47. The method of Claim 34 wherein the protein kinase is Tie-2.

48. The method of Claim 46 wherein the compound of Formula I, or physiologically acceptable salt, prodrug or biologically active metabolite thereof, is administered in combination with a pro-angiogenic growth factor.

49. The method of Claim 48 wherein the pro-angiogenic growth factor is selected from the group consisiting of VEGF, VEGF-B, VEGF-C, VEGF-D, VEGF-E, HGF, FGF-1, FGF-2, derivatives thereof and antiiodotypic antibodies.

50. The method of Claim 46 wherein the patient is suffering from anemia, ischemia, infarct, transplant rejection, a wound, gangrene or necrosis.

51. The method of Claim 33 wherein the protein kinase activity is involved in T cell activation, B cell activation, mast cell degranulation, monocyte activation, the potentiation of an inflammatory response or a combination thereof.

52. A compound according to Claim 1, wherein:

R_3 is H;

R_2 is $-Z^{101}-Z^{102}$;

Z^{101} is a covalent bond, $-(C_1-C_6)-$, $-(C_1-C_6)-O-$, $-(C_1-C_6)-C(O)-$, $-(C_1-C_6)-C(O)O-$, $-(C_1-C_6)-C(O)-NH-$, $-(C_1-C_6)-C(O)-N((C_1-C_6))-$ or a substituted phenyl group; and

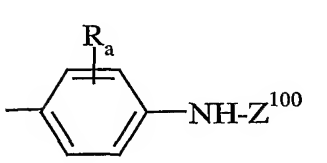
Z^{102} is hydrogen, a substituted or unsubstituted alkyl group or a substituted or unsubstituted, saturated or unsaturated heterocyclic group.

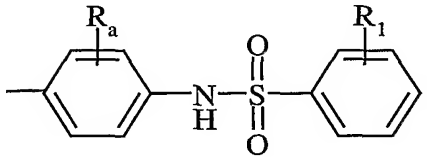
53. A compound according to Claim 52, wherein:

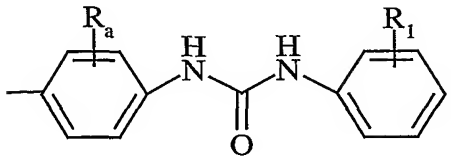
Z^{101} is selected from the group consisting of $-CH_2-C(O)O-$, $-CH_2-C(O)-$, $-CH_2-C(O)-NH-$, $-CH_2-C(O)-N(Me)-$, $-CH(Me)-C(O)O-$, $-(CH_2)_3-C(O)O-$, $-CH(Me)-C(O)-NH-$ and $-(CH_2)_3-C(O)-NH-$;

Z^{102} is selected from the group consisting of hydrogen, methyl, ethyl, N,N-dimethylaminoethyl, N,N-diethylaminoethyl, 2-phenyl-2-hydroxyethyl, morpholino, piperazinyl, N-methylpiperazinyl and 2-hydroxymethylpyrrolidinyl.

54. A compound according to Claim 53, wherein G is selected from



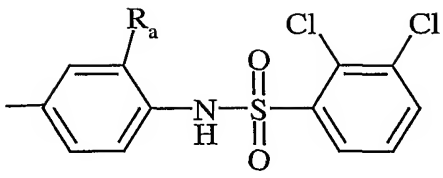
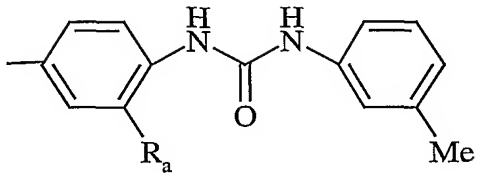
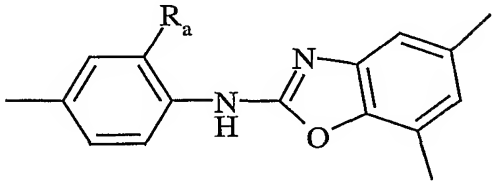
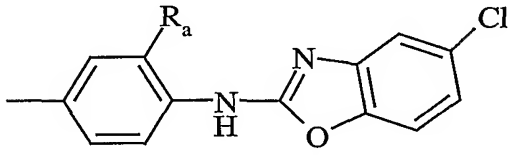
,


and


wherein:

Z^{100} is a substituted or unsubstituted benzoxazolyl or a substituted or unsubstituted benzthiazolyl.

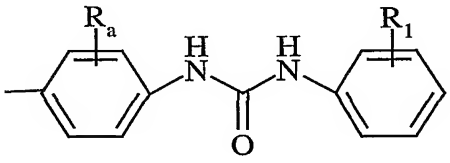
55. A compound according to Claim 8, 9, 10 or 53, wherein G is

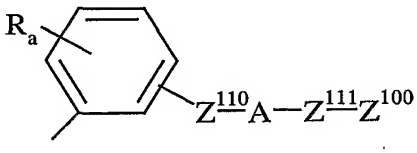

,

,

or


wherein there is only one R_a and it is H or F.

56. A compound according to Claim 52, wherein Z^{101} is a covalent bond; and Z^{102} is an optionally substituted pyridyl.

57. A compound according to Claim 56, wherein G is


.

58. A compound according to Claim 1, wherein R_3 is H;
R_2 is cyclopentyl; and
G is 
.

59. A compound according to Claim 58, wherein
Z^{110} is hydrogen;
A is O; and
Z^{100} is optionally substituted phenyl, furanyl or thienyl, where Z^{100} is

optionally substituted with one or more substituents each independently selected from the group consisting of F, COOH, NO_2, OMe, -COOMe, OCF_3 and CF_3.

60. A compound according to Claim 58, wherein:
Z^{110} is hydrogen;
A is -O-, -O-$(CR_2)_n$-C(O)- or -O-$(CR_2)_n$-O-;
n for each occurrence is 0 to 3;
Z^{100} is an optionally substituted group selected from the group consisting of cyclohexyl, phenyl, tetrahydropyranyl, tetrahydrofuranyl, isoxazolyl and piperidinyl; where Z^{100} is optionally substituted with one or more substituents selected from the group consisting of alkyl, alkoxy, halo, hydroxy and alkoxycarbonyl.

61. A compound according to Claim 58, wherein R^2 is an optionally substituted group selected from the group consisting of cyclobutyl and cyclohexyl.

62. A compound according to Claim 61, wherein R^2 is optionally substituted with one or more substituents selected from the group consisting of hydroxy, alkyl, hydroxyalkyl, carboxyalkyl and phenylalkoxyalkyl.

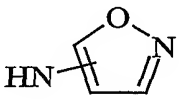
63. A compound according to Claim 62, wherein G is 4-phenoxyphenyl.

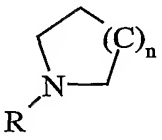
64. A compound according to Claim 6 wherein m is 2; a is 0; R_6 is H; b is 1 or 2; and R_4 and R_5 are each hydrogen.

65. A compound according to Claim 8, wherein m is 0, 1 or 2;
R_6 is hydrogen; R_5 is H or Y-Z;
Y is a covalent bond, -C(O)-, -$(CH_2)_q$O-, -$(CH_2)_q$-, -$(CH_2)_q$C(O)- or -C(O)$(CH_2)_q$-, where the alkyl portion of -$(CH_2)_q$O-, -$(CH_2)_q$-, -$(CH_2)_q$C(O)- and -C(O)$(CH_2)_q$- is optionally substituted by a halogen, hydroxy or an alkyl group; and

Z is hydrogen, alkyl, optionally substituted alkyl, alkoxyalkyl, optionally substituted heterocycloalkyl, optionally substituted heteroaryl, or optionally substituted amino.

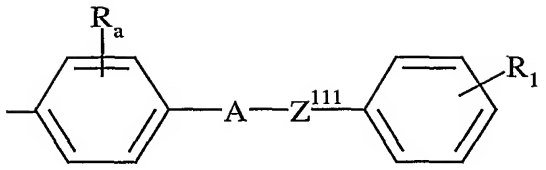
66. A compound according to Claim 65, wherein:

Z is hydrogen, methyl, ethyl, hydroxymethyl, methoxyethyl, N-methyl-piperidinyl, (t-butoxycarbonyl)(hydroxy)-piperidinyl, hydroxypiperidinyl, (hydroxymethyl)piperdinyl, (hydroxy)(methyl)-piperidinyl, morpholino, (methoxyethyl)piperizinyl, methylpiperizinyl, 4-piperidinylpiperidinyl, imidazolyl, methylimidazolyl, N-methylamino, N,N-dimethylamino, N-isopropylamino, N,N-diethylamino, 2,3-dihydroxypropylamino, 2-hydroxyethylamino, 3-hydroxypropylamino, methoxyethylamino, ethoxycarbonylmethylamino, phenylmethylamino, N-methyl-N-methoxyamino,  , furanylmethylamino, piperidinylethylamino, N-(2-N,N-dimethylaminoethyl)-N-methylamino, 2-N,N-dimethylaminoethylamino, N-methyl-N-(N-methylpiperidin-4-yl)amino, 2-morpholino-ethylamino, 3-morpholino-propylamino, 3-imidazolylpropylamino, or 3-(2-oxopyrrolidinyl)propylamino.

67. A compound according to Claim 8, wherein m is 2; R_5 is Y-Z; Y is -C(O)-; and Z is  where n is 0, 1, 2 or 3.

68. A compound according to Claim 9, wherein

R_4 is hydrogen or methyl;

G is  ;

A is selected from the group consisting of O, -N(R)- and -N(R)C(O)-;

Z^{111} is $-(CH_2)_n$-cycloalkyl-$(CH_2)_n$-;

R is hydrogen or alkyl;

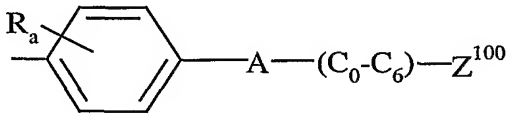
n is 0 to 5;

R_a is one or more substituents each independently selected from the group consisting of H, OH, F, Cl, methyl and methoxy; and

R_1 is one or more substituents each independently selected from the group consisting of H, CN, F, CF_3, OCF_3, methyl, methoxy and an optionally substituted amino group; where said amino group is optionally substituted with one or two groups each independently selected from the group consisting of alkyl, alkoxyalkyl, phenyl, substituted phenyl, and optionally substituted heteroaryl.

69. A compound according to Claim 68, wherein R_1 is 4-methylphenylthio or 2-pyridinylthio.

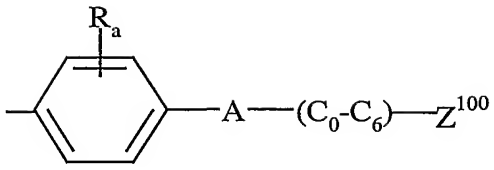
70. A compound according to Claim 9, wherein

G is 

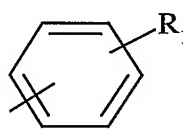
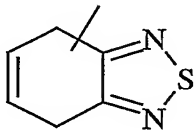
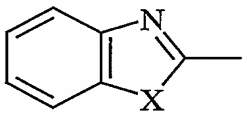
where Z^{100} is selected from the group consisting of benzo[b]thiophene, furanyl and thiophene.

71. A compound according to Claim 9, wherein R_a is alkoxy; A is -NH-C(O)-; and there is a covalent bond between A and Z^{100}.

72. A compound according to Claims 1, 8 or 9, wherein

G is  ;

A is selected from the group consisting of -N(R)-C(O)-N(R)-, -$(CH_2)_n$-N(R)C(O)N(R)-, -N(R)- and -N(R)-SO_2-; R is hydrogen or alkyl;

Z^{100} is  ,  ,  , pyridinyl, thiazolyl, furanyl, benzofuranyl or oxazolyl;

X is S, O or NR^1 where R^1 for each occurrence is independently H or Me;

R_a is one or more substituents each independently selected from the group consisting of H and F; and

R_1 is one or more substituents each independently selected from the group consisting of H, F, Cl, Br, NO_2, CF_3, alkyl, alkoxy and alkoxycarbonyl.

73. A compound according to Claim 72, wherein:

R_4 is methyl;

m is 1, 2 or 3;

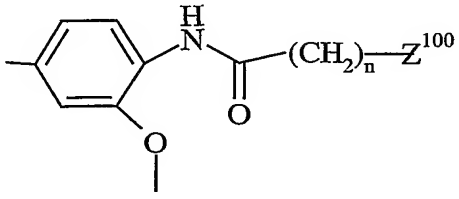
R_5 is Y-Z;

Y is -C(O)O-, -C(O)- or -C(O)-$(CH_2)_p$-; and

Z is aminoalkyl, N-alkylamino, N,N-dialkylamino or hydroxyalkylaminoalkyl.

74. A compound according to Claim 9, wherein

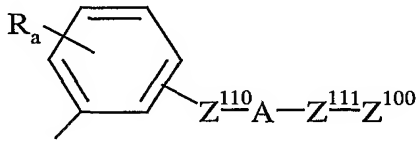
R_4 is methyl;

G is  ; wherein

n is 0 to 3; and

Z^{100} is an optionally substituted group selected from the group consisting of indolyl, indenyl, methylindenyl, methylindolyl, dimethylaminophenyl, phenyl, cyclohexyl and benzofuranyl.

75. A compound according to claim 9, wherein:

G is  ;

Z^{100} is an optionally substituted group selected from the group consisting of phenyl, imidazolyl, indolyl, furanyl, benzofuranyl and 2,3-dihydrobenzofuranyl; where Z^{100} is optionally substituted with one or more substituents each independently selected from the group consisting of F, Cl, CN, optionally substituted alkyl, -O-(optionally substituted alkyl), -COOH, $-Z^{105}-C(O)N(R)_2$, $-Z^{105}-N(R)-C(O)-Z^{200}$, $-Z^{105}-N(R)-S(O)_2-Z^{200}$, and $-Z^{105}-N(R)-C(O)-N(R)-Z^{200}$;

Z^{105} is a covalent bond or (C_1-C_6);

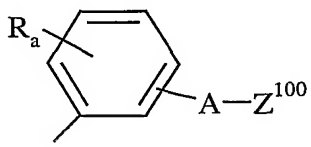
Z^{200} is an optionally substituted group selected from group consisting of (C_1-C_6), phenyl and $-(C_1-C_6)$-phenyl;

Z^{110} and Z^{111} are each independently a covalent bond or (C_1-C_3) group optionally substituted with alkyl, hydroxy, COOH, CN or phenyl; and

A is O, -N(R)-C(O)-N(R)-, -N(R)-C(O)-O-, -N(R)- or -N(R)-C(O)-, where R is H or alkyl.

76. A compound according to Claim 75, wherein R_4 is methyl.

77. A compound according to Claim 8, 9 or 10, wherein

G is  wherein:

Z^{100} is an optionally substituted group selected from the group consisting of benzoxazolyl, benzothiazolyl and benzimidazolyl.

78. A compound according to Claim 77, wherein;

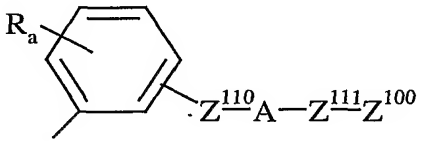
R_4 is methyl;

A is -NH-;

there is only one R_a and it is H or F; and

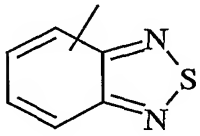
Z^{100} is optionally substituted with one or more substituents each independently selected from the group consisting of alkyl, halo, CF_3, and alkoxy.

79. A compound according to Claim 9, wherein:

G is 

;

Z^{100} is an optionally substituted group selected from the group consisting of phenyl, pyrrolyl, pyridyl, benzimidazolyl, naphthyl and



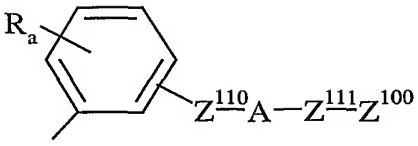
; where Z^{100} is optionally substituted with one or more substituents each independently selected from the group consisting of F, Cl, Br, NO_2, amino, N-alkylamino, N,N-dialkylamino, CN, optionally substituted alkyl, -O-(optionally substituted alkyl) and phenyl;

Z^{110} and Z^{111} for each occurrence is independently (C_0-C_3) optionally substituted with optionally substituted phenyl; and

A is -N(R)-C(O)-N(R)-, -N(R)-$S(O)_2$-, -N(R)-C(O)-, -N(R)- or -N(R)-C(O)-O-.

80. A compound according to Claim 79, wherein R_4 is methyl and there is only one R_a and it is F.

81. A compound according to Claim 9 or 66, wherein

G is  ;

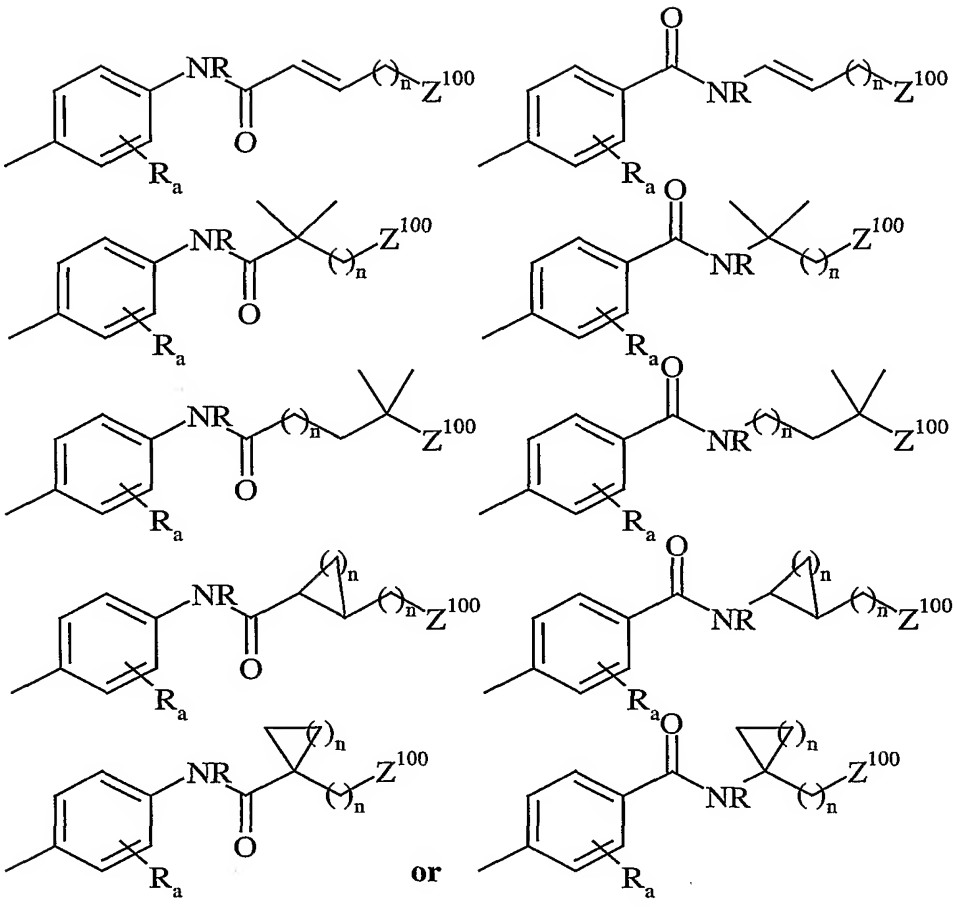
Z^{100} is an optionally substituted group selected from the group consisting of phenyl, isoxazolyl, tetrahydronaphthyl, furanyl, benzofuranyl, pyridyl and indolyl; where Z^{100} is optionally substituted with one or more substituents each independently selected from the group consisting of F, CN, NO_2, -C(O)H, $-CONH_2$, $-NHSO_2CF_3$, optionally substituted alkyl, optionally substituted heteroaryl and -O-(optionally substituted alkyl);

Z^{110} and Z^{111} are each independently optionally substituted (C_0-C_3); and

A is O, -N(R)-C(O)-$(CH_2)_n$-N(R)-, -C(O)-N(R)-, -N(R)-C(O)-O-, -N(R)-C(O)- or -N(R)-.

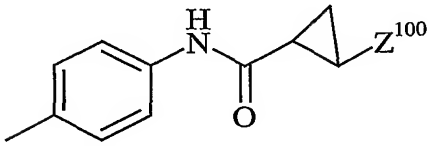
82. A compound according to Claim 81, wherein R_4 is methyl; R_a is H or methoxy; and Z^{110} and Z^{111} are each unsubstituted.

83. A compound according to Claim 9, wherein G is



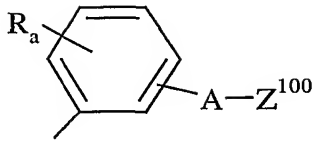
where R is H or lower alkyl and n is for each occurrence is independently 1 to 6.

84. A compound according to Claim 83, wherein G is



85. A compound according to Claim 84, wherein Z^{100} is substituted or unsubstituted phenyl.

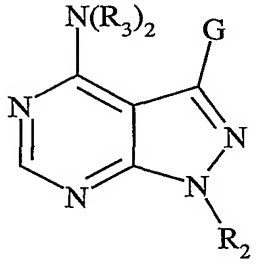
86. A compound according to Claim 8, 9 or 10, wherein

G is  where Z^{100} is an optionally substituted group selected from the group consisting of benzoxazolyl, benzothiazolyl and benzimidazolyl.

87. A compound according to Claim 11 wherein n is 2; R_6 is H; m is 1; r is 1; and R_4 and R_5 are each hydrogen.

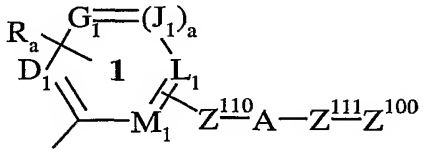
88. A compound according to claim 64 or 87 wherein G is 4-phenoxyphenyl.

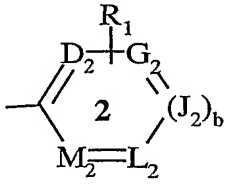
89. A compound of Formula (I)

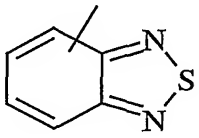
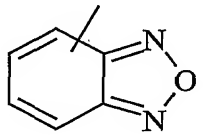
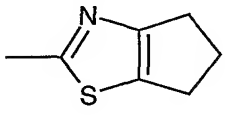


(I)

racemic-diastereomeric mixtures, optical isomers, pharmaceutically-acceptable salts, prodrugs or biologically active metabolites thereof wherein:

G is 

where Z^{100} is  or a group optionally substituted with R_1 selected from the group consisting of alkyl, cycloalkyl, pyrrolidinyl,

quinolinyl, quinoxalinyl, quinazolinyl, isoquinolinyl, phthalazinyl, imidazo[1,2-a]pyrimidinyl, 1H-imidazo[1,2-a]imidazolyl, imidazo[2,1-b][1,3]thiazolyl, naphthyl, tetrahydronaphthyl, benzothienyl, furanyl, thienyl, benzoxazolyl, benzoisoxazolyl, benzothiazolyl,  ,  ,  , thiazolyl, benzofuranyl, 2,3-dihydrobenzofuranyl, indolyl, isoxazolyl, tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, pyrazolyl, pyrrolyl, pyrrolopyridinyl, H-pyridinone, oxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, indolinyl, indazolyl, imidazo[1,2-a]pyridinyl, benzoisothiazolyl, 1,1-dioxybenzoisothiazolyl, pyrido-oxazolyl, pyrido-thiazolyl, pyrimido-oxazolyl, pyrimido-thiazolyl and benzimidazolyl;

Z^{110} is a covalent bond, or an optionally substituted (C_1-C_6) which is optionally substituted with one or more substituents selected from the group consisting of alkyl, CN, OH, halogen, NO_2, COOH, substituted or unsubstituted amino and substituted or unsubstituted phenyl;

Z^{111} is a covalent bond, an optionally substituted (C_1-C_6) or an optionally substituted -$(CH_2)_n$-cycloalkyl-$(CH_2)_n$-; where the optionally substituted groups are optionally substituted with one or more substituents selected from the group consisting of alkyl, CN, OH, halogen, NO_2, COOH, substituted or unsubstituted amino and substituted or unsubstituted phenyl;

R_a and R_1 each represent one or more substituents for each occurrence independently selected from the group consisting of hydrogen, halogen, -CN, -NO_2, -C(O)OH, -C(O)H, -OH, -C(O)O-alkyl, -C(O)O-aryl, -C(O)O-heteroaryl, -C(O)-alkyl, -C(O)-aryl, -C(O)-heteroaryl, substituted or unsubstituted carboxamido, tetrazolyl, trifluoromethylcarbonylamino, trifluoromethylsulfonamido, substituted or unsubstituted alkyl, substituted or unsubstituted

cycloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryloxy, substituted or unsubstituted heteroaryloxy, substituted or unsubstituted heteroarylalkoxy, substituted or unsubstituted arylalkoxy, substituted or unsubstituted alkyl-$S(O)_p$-, substituted or unsubstituted alkyl-S-, substituted or unsubstituted aryl-$S(O)_p$-, substituted or unsubstituted heteroaryl-$S(O)_p$-, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted alkynyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted amido groups, substituted or unsubstituted heteroarylthio, substituted or unsubstituted arylthio, $-Z^{105}$-C(O)N$(R)_2$, $-Z^{105}$-N(R)-C(O)-Z^{200}, $-Z^{105}$-N(R)-$S(O)_2$-Z^{200}, $-Z^{105}$-N(R)-C(O)-N(R)-Z^{200}, R_c and CH_2OR_c;

where R_c for each occurrence is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, $-CH_2$-NR_dR_e, -W-$(CH_2)_t$-NR_dR_e, -W-$(CH_2)_t$-O-alkyl, -W-$(CH_2)_t$-S-alkyl, or -W-$(CH_2)_t$-OH;

Z^{105} for each occurrence is independently a covalent bond or (C_1-C_6);

Z^{200} for each occurrence is independently a substituted or unsubstituted (C_1-C_6), substituted or unsubstituted phenyl or substituted or unsubstituted -(C_1-C_6)-phenyl;

R_d and R_e for each occurrence are independently H, alkyl, alkanoyl or SO_2-alkyl; or R_d, R_e and the nitrogen atom to which they are attached together form a five- or six-membered heterocyclic ring;

t for each occurrence is independently an integer from 2 to 6;

W for each occurrence is independently a direct bond or O, S, S(O), $S(O)_2$, or NR_f, wherein R_f for each occurrence is independently H or alkyl; or

R_1 is a substituted or unsubstituted carbocyclic or heterocyclic ring fused with ring 2;

R_3 for each occurrence is, independently, hydrogen, hydroxy, substituted or unsubstituted alkyl, substituted or unsubstituted -C(O)-alkyl, a

substituted or unsubstituted -C(O)-aryl, or a substituted or unsubstituted –C(O)-heteroaryl or substituted or unsubstituted alkoxy;

A is $-(C_1-C_6)$-, -O-; -S-; $-S(O)_p$-; -N(R)-; -N(C(O)OR)-; -N(C(O)R)-; -$N(SO_2R)$-; $-CH_2O$-; $-CH_2S$-; $-CH_2N(R)$-; -CH(NR)-; $-CH_2N(C(O)R)$-; $-CH_2N(C(O)OR)$-; $-CH_2N(SO_2R)$-; -CH(NHR)-; -CH(NHC(O)R)-; -$CH(NHSO_2R)$-; -CH(NHC(O)OR)-; -CH(OC(O)R)-; -CH(OC(O)NHR)-; -CH=CH-; -C(=NOR)-; -C(O)-; -CH(OR)-; -C(O)N(R)-; -N(R)C(O)-; $-N(R)S(O)_p$-; -OC(O)N(R)-; ; $-N(R)-C(O)-(CH_2)_n-N(R)$-, -N(R)C(O)O-; $-N(R)-(CH_2)_{n+1}-C(O)$-, $-S(O)_pN(R)$-; $-O-(CR_2)_{n+1}-C(O)$-, $-O-(CR_2)_{n+1}-O$-, $-N(C(O)R)S(O)_p$-; $-N(R)S(O)_pN(R)$-; $-N(R)-C(O)-(CH_2)_n-O$-, -C(O)N(R)C(O)-; $-S(O)_pN(R)C(O)$-; $-OS(O)_pN(R)$-; $-N(R)S(O)_pO$-; $-N(R)S(O)_pC(O)$-; $-SO_pN(C(O)R)$-; $-N(R)SO_pN(R)$-; -C(O)O-; $-N(R)P(OR_b)O$-; $-N(R)P(OR_b)$-; $-N(R)P(O)(OR_b)O$-; $-N(R)P(O)(OR_b)$-; $-N(C(O)R)P(OR_b)O$-; $-N(C(O)R)P(OR_b)$-; $-N(C(O)R)P(O)(OR_b)O$-, or $-N(C(O)R)P(OR_b)$-;

where R for each occurrence is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl or substituted or unsubstituted aryl;

R_b for each occurrence is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl or substituted or unsubstituted aryl;

p is 1 or 2; or

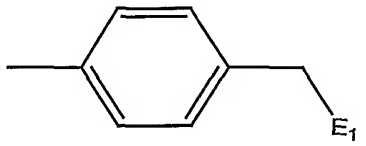
in a phosphorus containing group, the nitrogen atom, the phosphorus atom, R and R_b together form a five- or six-membered heterocyclic ring; or

A is $NRSO_2$ and R, R_a and the nitrogen atom together form a substituted or unsubstituted five or-six-membered heterocyclic ring fused to ring 1; or

Z^{110}-A-Z^{111} taken together is a covalent bond; and

R_2 is a) hydrogen; b) substituted or unsubstituted trityl; c) substituted or unsubstituted cycloalkenyl; d) azaheteroaryl substituted with a substituted or unsubstituted alkyl; e) azacycloalkyl which is substituted with one or more substituents selected from substituted or

unsubstituted –(C_1-C_6)-alkyl, substituted or unsubstituted -C_1-C_6-alkyl-OR, substituted or unsubstituted –C(O)-C_1-C_6-alkyl-N($R)_2$, substituted or unsubstituted –C_1-C_6-alkyl-N($R)_2$, substituted or unsubstituted -C_1-C_6-alkyl-cycloalkyl, substituted or unsubstituted tetrahydrothienyl, and substituted or unsubstituted tetrahydrothiopyranyl; or f) a group of the formula



wherein E_1 is piperidinyl, piperazinyl, imidazolyl, morpholinyl, pyrrolidinyl, amino, amido, or tetrahydrothiazolyl, and wherein E is optionally substituted with one or more substituents selected from –C_0-C_6-alkyl-OR, -C_1-C_6-alkyl-C(O)OR, -C_1-C_6-alkyl-heteroaryl, -C_1-C_6-alkyl-heterocycloalkyl, and –C_1-C_6-alkyl-N($R)_2$;

a is 1 and D_1, G_1, J_1, L_1 and M_1 are each independently selected from the group consisting of CR_a and N, provided that at least two of D_1, G_1, J_1, L_1 and M_1 are CR_a; or

a is 0, and one of D_1, G_1, L_1 and M_1 is NR_a, one of D_1, G_1, L_1 and M_1 is CR_a and the remainder are independently selected from the group consisting of CR_a and N, wherein R_a is as defined above;

b is 1 and D_2, G_2, J_2, L_2 and M_2 are each independently selected from the group consisting of CR_a and N, provided that at least two of D_2, G_2, J_2, L_2 and M_2 are CR_a; or

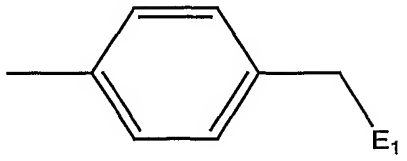
b is 0, and one of D_2, G_2, L_2 and M_2 is NR_a, one of D_2, G_2, L_2 and M_2 is CR_a and the remainder are independently selected from the group consisting of CR_a and N, wherein R_a is as defined above; and

n for each occurrence is independently an integer from 0 to 6;

provided that when Z^{110}-A-Z^{111} taken together are a covalent bond, then Z^{100} is not alkyl; and

provided that when Z^{110}-A-Z^{111} taken together are a C_1-C_6 alkyl, then Z^{100} is not phenyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, furyl or thienyl.

90. The compound of Claim 89, wherein R_2 is a group represented by the following structural formula:



wherein:

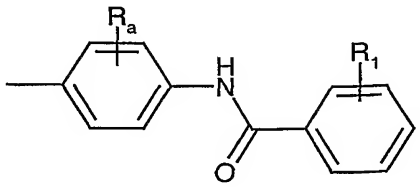
E_1 is selected from the group consisting of –amino-C_1-C_6-alkyl-morpholino, -piperidino-(C_1-C_6-alkyl-OR), -imidazolyl-C_1-C_6-alkyl-C(O)OR, -piperazino-C_1-C_6-alkyl-OR, -amino-C_1-C_6-alkyl-OR, -pyrrolidino-OR, -amino-C_1-C_6-alkyl-imidazolo, -amino-C_1-C_6-alkyl-$N(R)_2$, -amido-C_1-C_6-alkyl-$N(R)_2$, tetrahydrothiazolyl, N,N-di-(hydroxy-C_1-C_6-alkyl)amino-, and –piperizino-OR.

91. The compound of Claim 90, wherein:

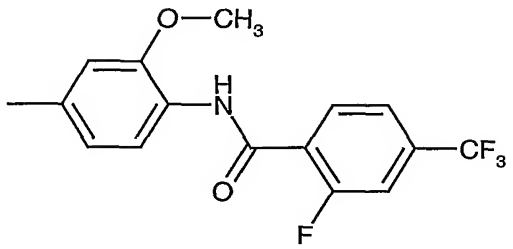
E_1 is selected from the group consisting of 4-(2-hydroxyethyl)morpholino, 3-hydroxymethylpiperidino, 2-[3-(methylcarboxy)propyl]imidizol-4-yl, 4-(2-hydroxyethyl)piperazino, 2-hydroxyethylamino, 3-hydroxypyrrolidino, 3-imidazolopropylamino, 4-hydroxybutylamino, 3-methoxypropylamino, 3-(N,N-dimethylamino)propylamino, N-[2-(N,N-dimethyl)ethyl]amido, tetrahydrothiazolyl, N,N-di-(2-hydroxyethyl)amino, 4-hydroxypiperizino, and 4-hydroxymethylpiperizino.

92. The compound of Claim 90, wherein Z^{110}-A-Z^{111} is –NHC(O)-.

93. The compound of Claim 90, wherein G is a group represented by the following structural formula:



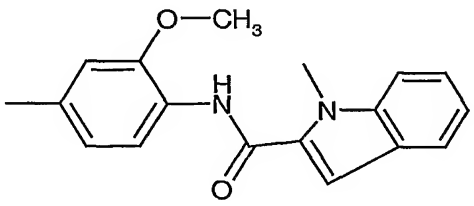
94. The compound of Claim 93, wherein G is represented by the following structural formula:



95. The compound of Claim 89, wherein R_2 is an azaheteroaryl substituted with a C_1-C_6 alkyl, wherein the alkyl is optionally substituted with with one or more substitutents selected form RO-, -C(O)OR, -C(O)N($R)_2$, and -N($R)_2$.

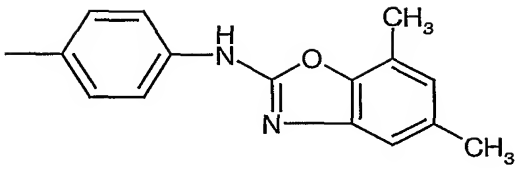
96. The compound of Claim 95, wherein R_2 is 4-(2-hydroxyethyl)pyridin-2-yl, 3-aminomethylpyridin-4-yl or 2-methylimidazol-4-yl.

97. The compound of Claim 96, wherein G is represented by the following formula:



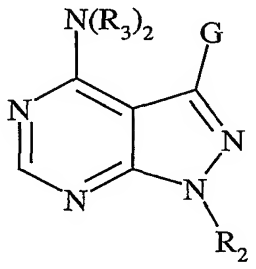
98. The compound of Claim 89, wherein R_2 is a pyrrolidinyl which is substituted with 2-methoxyethyl, N,N-dimethylaminomethyl, N,N-dimethylamino-1-oxoethyl, or 2-(N-methylamino)-1-oxopropyl.

99. The compound of Claim 98 wherein G is represented by the following structural formula:



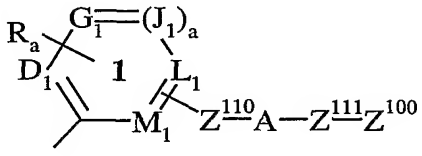
100. The compound of Claim 89, wherein R_2 is a piperidinyl which is substituted with a tetrahydrothiopyranyl, tetrahydrothienyl, 2-(N-methylamino)-2-methyl-1-oxopropyl, 2-methoxyethyl, or cyclopropylmethyl.

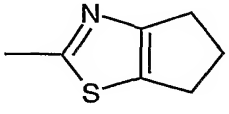
101. A compound of Formula (I)



(I)

racemic-diastereomeric mixtures, optical isomers, pharmaceutically-acceptable salts, prodrugs or biologically active metabolites thereof wherein:

G is  ;

wherein Z^{100} is pyrrolidinyl, quinolinyl, quinoxalinyl, quinazolinyl, isoquinolinyl, phthalazinyl, imidazo[1,2-a]pyrimidinyl, 1H-imidazo[1,2-a]imidazolyl, imidazo[2,1-b][1,3]thiazolyl, H-pyridinone, 1,1-dioxybenzoisothiazolyl, benzoisoxazolyl, alkyl, imidazo[1,2-a]pyridinyl, pyrrolopyridinyl or  , wherein all of the foregoing Z^{100} groups are optionally substituted with R_1;

Z^{110} is a covalent bond, or an optionally substituted (C_1-C_6) which is optionally substituted with one or more substituents selected from the group consisting of alkyl, CN, OH, halogen, NO_2, COOH, substituted or unsubstituted amino and substituted or unsubstituted phenyl;

Z^{111} is a covalent bond, an optionally substituted (C_1-C_6) or an optionally substituted -$(CH_2)_n$-cycloalkyl-$(CH_2)_n$-; where the optionally substituted groups are optionally substituted with one or more substituents selected from the group consisting of alkyl, CN, OH, halogen, NO_2, COOH, substituted or unsubstituted amino and substituted or unsubstituted phenyl;

R_a and R_1 each represent one or more substituents for each occurrence independently selected from the group consisting of hydrogen, halogen, -CN, -NO_2, -C(O)OH, -C(O)H, -OH, -C(O)O-alkyl, -C(O)O-aryl, -C(O)O-heteroaryl, -C(O)-alkyl, -C(O)-aryl, -C(O)-heteroaryl, substituted or unsubstituted carboxamido, tetrazolyl, trifluoromethylcarbonylamino, trifluoromethylsulfonamido, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryloxy, substituted or unsubstituted heteroaryloxy, substituted or unsubstituted heteroarylalkoxy, substituted or unsubstituted arylalkoxy, substituted or unsubstituted alkyl-$S(O)_p$-, substituted or unsubstituted alkyl-S-, substituted or unsubstituted aryl-$S(O)_p$-, substituted or unsubstituted heteroaryl-$S(O)_p$-, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted alkynyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted amido groups, substituted or unsubstituted heteroarylthio, substituted or unsubstituted arylthio, -Z^{105}-C(O)N$(R)_2$, -Z^{105}-N(R)-C(O)-Z^{200}, -Z^{105}-N(R)-$S(O)_2$-Z^{200}, -Z^{105}-N(R)-C(O)-N(R)-Z^{200}, R_c and CH_2OR_c;

where R_c for each occurrence is independently hydrogen, substituted or

unsubstituted alkyl, substituted or unsubstituted aryl, $-CH_2-NR_dR_e$, $-W-(CH_2)_t-NR_dR_e$, $-W-(CH_2)_t-O$-alkyl, $-W-(CH_2)_t-S$-alkyl, or $-W-(CH_2)_t-OH$;

Z^{105} for each occurrence is independently a covalent bond or (C_1-C_6);

Z^{200} for each occurrence is independently a substituted or unsubstituted (C_1-C_6), substituted or unsubstituted phenyl or substituted or unsubstituted $-(C_1-C_6)$-phenyl;

R_d and R_e for each occurrence are independently H, alkyl, alkanoyl or SO_2-alkyl; or R_d, R_e and the nitrogen atom to which they are attached together form a five- or six-membered heterocyclic ring;

t for each occurrence is independently an integer from 2 to 6;

W for each occurrence is independently a direct bond or O, S, S(O), $S(O)_2$, or NR_f, wherein R_f for each occurrence is independently H or alkyl; or

R_1 is a substituted or unsubstituted carbocyclic or heterocyclic ring fused with ring 2;

R_3 for each occurrence is, independently, hydrogen, hydroxy, substituted or unsubstituted alkyl, substituted or unsubstituted -C(O)-alkyl, a substituted or unsubstituted -C(O)-aryl, or a substituted or unsubstituted –C(O)-heteroaryl or substituted or unsubstituted alkoxy;

A is $-(C_1-C_6)$ -, -O-; -S-; $-S(O)_p-$; -N(R)-; -N(C(O)OR)-; -N(C(O)R)-; $-N(SO_2R)-$; $-CH_2O-$; $-CH_2S-$; $-CH_2N(R)-$; -CH(NR)-; $-CH_2N(C(O)R))-$; $-CH_2N(C(O)OR)-$; $-CH_2N(SO_2R)-$; -CH(NHR)-; -CH(NHC(O)R)-; $-CH(NHSO_2R)-$; -CH(NHC(O)OR)-; -CH(OC(O)R)-; -CH(OC(O)NHR)-; -CH=CH-; -C(=NOR)-; -C(O)-; -CH(OR)-; -C(O)N(R)-; -N(R)C(O)-; $-N(R)S(O)_p-$; $-OC(O)N(R)-$; ; $-N(R)-C(O)-(CH_2)_n-N(R)-$, -N(R)C(O)O-; $-N(R)-(CH_2)_{n+1}-C(O)-$, $-S(O)_pN(R)-$; $-O-(CR_2)_{n+1}-C(O)-$, $-O-(CR_2)_{n+1}-O-$, $-N(C(O)R)S(O)_p-$; $-N(R)S(O)_pN(R)-$; $-N(R)-C(O)-(CH_2)_n-O-$, -C(O)N(R)C(O)-; $-S(O)_pN(R)C(O)-$; $-OS(O)_pN(R)-$; $-N(R)S(O)_pO-$; $-N(R)S(O)_pC(O)-$; $-SO_pN(C(O)R)-$; $-N(R)SO_pN(R)-$; -C(O)O-; $-N(R)P(OR_b)O-$; $-N(R)P(OR_b)-$; $-N(R)P(O)(OR_b)O-$; $-N(R)P(O)(OR_b)-$; $-N(C(O)R)P(OR_b)O-$; $-N(C(O)R)P(OR_b)-$; $-N(C(O)R)P(O)(OR_b)O-$, or

$-N(C(O)R)P(OR_b)-$;

where R for each occurrence is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl or substituted or unsubstituted aryl;

R_b for each occurrence is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl or substituted or unsubstituted aryl;

p is 1 or 2; or

in a phosphorus containing group, the nitrogen atom, the phosphorus atom, R and R_b together form a five- or six-membered heterocyclic ring; or

A is $NRSO_2$ and R, R_a and the nitrogen atom together form a substituted or unsubstituted five or-six-membered heterocyclic ring fused to ring 1; or

Z^{110}-A-Z^{111} taken together is a covalent bond; and

R_2 is H or a group of the formula $-Z^{101}-Z^{102}$;

Z^{101} is a covalent bond, $-(C_1-C_6)-$, $-(C_1-C_6)-$ $-O-$, $-(C_1-C_6)-$ $-C(O)-$, $-(C_1-C_6)-$ $-C(O)O-$, $-(C_1-C_6)-C(O)-NH-$, $-(C_1-C_6)-C(O)-N((C_1-C_6))-$ or a substituted or unsubstituted phenyl group;

Z^{102} is hydrogen; a substituted or unsubstituted alkyl group; a substituted or unsubstituted cycloalkyl group; a substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted, saturated or unsaturated heterocyclic group; or a substituted or unsubstituted, saturated or unsaturated heterobicyclic group; wherein said substituted alkyl, substituted cycloalkyl, substituted cycloalkenyl, substituted heterocyclic and substituted heterobicyclic group having one or more substituents each independently selected from the group consisting of hydroxyl, cyano, nitro, halo, substituted or unsubstituted (C_1-C_6), substituted or unsubstituted aryl, substituted or unsubstituted -C(O)-alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted $-N(R)-(C_1-C_6)$ -OR, substituted or unsubstituted $-N((C_1-C_6)$ $-OR)_2$,substituted or unsubstituted $-N(R)-(C_1-C_6)$ $-C(O)_2R$, substituted or unsubstituted $-(C_1-C_6)$ $-N(R)-(C_1-C_6)$ -OR, substituted or unsubstituted $-(C_1-C_6)$ $-N(R)-(C_1-C_6)$ $-N(R)_2$, substituted or unsubstituted $-(C_1-C_6)$ $-C(O)N(R)-(C_1-C_6)$ $-N(R)_2$, substituted or

unsubstituted sulfonamido, substituted or unsubstituted ureido, substituted or unsubstituted carboxamido, substituted or unsubstituted amino, substituted or unsubstituted –N(R)-(C_1-C_6) -OR, oxo, and a saturated, unsaturated or aromatic, substituted or unsubstituted heterocyclic group comprising one or more heteroatoms selected from the group consisting of N, O, and S; wherein the nitrogen atoms of said heterocyclic group or heterobicyclic group are independently optionally substituted by oxo, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted -C(O)N($R)_2$, substituted or unsubstituted -C(O)-(C_1-C_6)-N($R)_2$, -C(O)-alkyl, -C(O)-aryl, -C(O)-heteroaryl, substituted or unsubstituted arylalkyl group, or substituted or unsubstituted heteroarylalkyl; or

R_2 is a group of the formula -B-E, wherein B is a substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted azacycloalkyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkylsulfonyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aminoalkylcarbonyl, substituted or unsubstituted alkylene, substituted or unsubstituted aminoalkyl, substituted or unsubstituted alkylenecarbonyl or substituted or unsubstituted aminoalkylcarbonyl group; and E is substituted or unsubstituted alkyl, a substituted or unsubstituted cycloalkyl, substituted or unsubstituted azacycloalkyl, a substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted (C_1-C_6)-azacycloalkyl-, substituted or unsubstituted azacycloalkylcarbonyl, substituted or unsubstituted azacycloalkylsulfonyl, substituted or unsubstituted azacycloalkylalkyl, substituted or unsubstituted heteroaryl-N(R)-(C_1-C_6)-, substituted or unsubstituted aryl-N(R)-(C_1-C_6)-, substituted or unsubstituted alkyl-N(R)-(C_1-C_6)-, substituted or unsubstituted heteroaryl-(C_1-C_6)-N(R)-, substituted or unsubstituted aryl-(C_1-C_6)-N(R)-, substituted or unsubstituted alkyl-(C_1-C_6)-N(R)-, substituted

or unsubstituted heteroaryl, substituted or unsubstituted heteroarylcarbonyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted arylcarbonyl, substituted or unsubstituted heteroarylsulfonyl, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted arylsulfonyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted azacycloalkylcarbonylamino, substituted or unsubstituted heteroarylcarbonylamino, substituted or unsubstituted arylcarbonylamino, substituted or unsubstituted alkylcarbonylamino or substituted or unsubstituted aryl;

a is 1 and D_1, G_1, J_1, L_1 and M_1 are each independently selected from the group consisting of CR_a and N, provided that at least two of D_1, G_1, J_1, L_1 and M_1 are CR_a; or

a is 0, and one of D_1, G_1, L_1 and M_1 is NR_a, one of D_1, G_1, L_1 and M_1 is CR_a and the remainder are independently selected from the group consisting of CR_a and N, wherein R_a is as defined above;

b is 1 and D_2, G_2, J_2, L_2 and M_2 are each independently selected from the group consisting of CR_a and N, provided that at least two of D_2, G_2, J_2, L_2 and M_2 are CR_a; or

b is 0, and one of D_2, G_2, L_2 and M_2 is NR_a, one of D_2, G_2, L_2 and M_2 is CR_a and the remainder are independently selected from the group consisting of CR_a and N, wherein R_a is as defined above; and

n for each occurrence is independently an integer from 0 to 6;

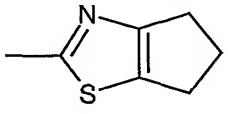
provided that when A is –N(R)-, Z^{110} and Z^{111} are each a covalent bond, and R_2 is a 3,4-dihydroxytetrahydrofur-2-yl or a 3,4-diacyloxytetrahydrofur-2-yl, then Z^{100} is not alkyl, tetrahydropyranyl, tetrahydrofuranyl, piperidinyl or pyrrolidinyl;

provided that when Z^{110} and Z^{111} are each a covalent bond, and R_2 is a 3,4-dihydroxytetrahydrofur-2-yl or a 3,4-diacyloxytetrahydrofur-2-yl, Z^{100} is a substituted or unsubstituted alkyl, then A is not alkyl, -O-, -C(O)-, -NHC(O)- or –C(O)O-;

provided that when Z^{110}-A-Z^{111} taken together are a covalent bond, then Z^{100} is not alkyl;

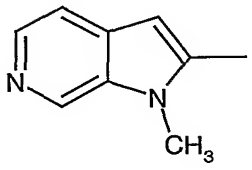
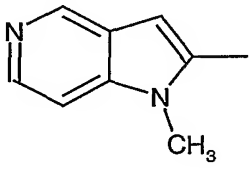
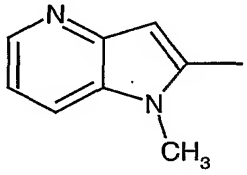
provided that when Z^{110}-A-Z^{111} taken together are a C_1-C_6 alkyl, then Z^{100} is not phenyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, furyl or thienyl; and

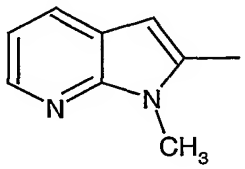
provided that when R_2 is a substituted or unsubstituted cyclopentyl, Z^{100} is an substituted or unsubstituted alkyl, Z^{110} and Z^{111} are each a covalent bond, then A is not –O-, -C(O)O-, or –N(R)-.

102. The compound of Claim 101, wherein Z^{100} is 2-pyrrolidinyl, 1,2-dihydro-2-oxopyridin-3-yl, benzoisoxazol-3-yl, 1,1-dioxybenzoisothiazol-3-yl, imidazo[1,2-a]pyridin-2-yl or  and R_2 is 4-(4-methylpiperazino)-cyclohexyl.

103. The compound of Claim 102, wherein Z^{110}-A-Z^{111} is –NH-.

104. The compound of Claim 101, wherein Z^{100} is a pyrrolopyridinyl selected from

 ,  , 

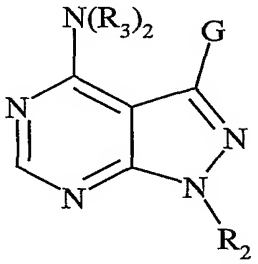
or 

105. The compound of Claim 104, wherein Z^{110}-A-Z^{111} is –NHC(O)-.

106. The compound of Claim 105, wherein R_2 is piperdin-4-yl, N-methylpiperidin-4-yl, N-(prop-2-yl)piperidin-4-yl, N-(imidazol-4-yl-methyl)piperidin-4-yl, N-(2-methylimidazol-4-yl-methyl)piperidin-4-yl, N-

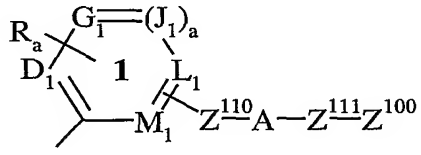
(pyrazol-4-yl-methyl)piperidin-4-yl, N-(2-methoxyethyl)piperidin-4-yl, N-(fur-3-yl-methyl)piperidin-4-yl, N-(tetrahydropyran-4-yl-methyl)piperidin-4-yl, N-(pyrrol-2-yl-methyl)piperidin-4-yl, or N-(2-difluoroethyl)piperidin-4-yl.

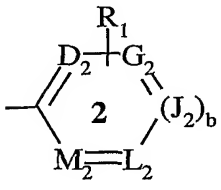
107. A compound of Formula (I)

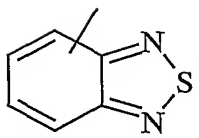
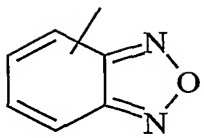
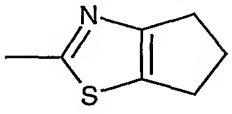


(I)

racemic-diastereomeric mixtures, optical isomers, pharmaceutically-acceptable salts, prodrugs or biologically active metabolites thereof wherein:

G is 

where Z^{100} is  or a group optionally substituted with R_1 selected from the group consisting of alkyl, cycloalkyl, pyrrolidinyl, quinolinyl, quinoxalinyl, quinazolinyl, isoquinolinyl, phthalazinyl, imidazo[1,2-a]pyrimidinyl, 1H-imidazo[1,2-a]imidazolyl, imidazo[2,1-b][1,3]thiazolyl, naphthyl, tetrahydronaphthyl, benzothienyl, furanyl, thienyl, benzoxazolyl, benzoisoxazolyl,

benzothiazolyl,  ,  ,  , thiazolyl, benzofuranyl, 2,3-dihydrobenzofuranyl, indolyl, isoxazolyl, tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, pyrazolyl, pyrrolyl, pyrrolopyridinyl, H-pyridinone, oxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, indolinyl, indazolyl, imidazo[1,2-a]pyridinyl, benzoisothiazolyl, 1,1-dioxybenzoisothiazolyl, pyrido-oxazolyl, pyrido-thiazolyl, pyrimido-oxazolyl, pyrimido-thiazolyl and benzimidazolyl;

Z^{110} is a covalent bond, or an optionally substituted (C_1-C_6) which is optionally substituted with one or more substituents selected from the group consisting of alkyl, CN, OH, halogen, NO_2, COOH, substituted or unsubstituted amino and substituted or unsubstituted phenyl;

Z^{111} is a covalent bond, an optionally substituted (C_1-C_6) or an optionally substituted -$(CH_2)_n$-cycloalkyl-$(CH_2)_n$-; where the optionally substituted groups are optionally substituted with one or more substituents selected from the group consisting of alkyl, CN, OH, halogen, NO_2, COOH, substituted or unsubstituted amino and substituted or unsubstituted phenyl;

R_a and R_1 each represent one or more substituents for each occurrence independently selected from the group consisting of hydrogen, -C(O)O-aryl, -C(O)O-heteroaryl, -C(O)-alkyl, -C(O)-aryl, -C(O)-heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylalkoxy, substituted or unsubstituted arylalkoxy, substituted or unsubstituted alkyl-$S(O)_p$-, substituted or unsubstituted alkyl-S-, substituted or unsubstituted aryl-$S(O)_p$-, substituted or unsubstituted heteroaryl-$S(O)_p$-, and wherein at least one of R_a and R_1 is not hydrogen;

R_3 for each occurrence is, independently, hydrogen, hydroxy, substituted or

unsubstituted alkyl, substituted or unsubstituted -C(O)-alkyl, a substituted or unsubstituted -C(O)-aryl, or a substituted or unsubstituted –C(O)-heteroaryl or substituted or unsubstituted alkoxy;

A is –(C_1-C_6) -, -O-; -S-; -$S(O)_p$-; -N(R)-; -N(C(O)OR)-; -N(C(O)R)-; -$N(SO_2R)$-; -CH_2O-; -CH_2S-; -$CH_2N(R)$-; -CH(NR)-; -$CH_2N(C(O)R)$)-; -$CH_2N(C(O)OR)$-; -$CH_2N(SO_2R)$-; -CH(NHR)-; -CH(NHC(O)R)-; -$CH(NHSO_2R)$-; -CH(NHC(O)OR)-; -CH(OC(O)R)-; -CH(OC(O)NHR)-; -CH=CH-; -C(=NOR)-; -C(O)-; -CH(OR)-; -C(O)N(R)-; -N(R)C(O)-; -$N(R)S(O)_p$-; -OC(O)N(R)-; ; -N(R)-C(O)-$(CH_2)_n$-N(R)-, -N(R)C(O)O-; -N(R)-$(CH_2)_{n+1}$-C(O)-, -$S(O)_pN(R)$-; -O-$(CR_2)_{n+1}$-C(O)-, -O-$(CR_2)_{n+1}$-O-, -N(C(O)R)$S(O)_p$-; -$N(R)S(O)_pN(R)$-; -N(R)-C(O)-$(CH_2)_n$-O-, -C(O)N(R)C(O)-; -$S(O)_pN(R)C(O)$-; -$OS(O)_pN(R)$-; -$N(R)S(O)_pO$-; -$N(R)S(O)_pC(O)$-; -$SO_pN(C(O)R)$-; -$N(R)SO_pN(R)$-; -C(O)O-; -$N(R)P(OR_b)O$-; -$N(R)P(OR_b)$-; -$N(R)P(O)(OR_b)O$-; -$N(R)P(O)(OR_b)$-; -$N(C(O)R)P(OR_b)O$-; -$N(C(O)R)P(OR_b)$-; -$N(C(O)R)P(O)(OR_b)O$-, or -$N(C(O)R)P(OR_b)$-;

where R for each occurrence is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl or substituted or unsubstituted aryl;

R_b for each occurrence is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl or substituted or unsubstituted aryl;

p is 1 or 2; or

in a phosphorus containing group, the nitrogen atom, the phosphorus atom, R and R_b together form a five- or six-membered heterocyclic ring; or

A is $NRSO_2$ and R, R_a and the nitrogen atom together form a substituted or unsubstituted five or-six-membered heterocyclic ring fused to ring 1; or

Z^{110}-A-Z^{111} taken together is a covalent bond; and

R_2 is H or a group of the formula -Z^{101}-Z^{102};

Z^{101} is a covalent bond, -(C_1-C_6)-, -(C_1-C_6)- -O-, -(C_1-C_6)- -C(O)-, -(C_1-C_6)- -C(O)O-, -(C_1-C_6)-C(O)-NH-, -(C_1-C_6)-C(O)-N((C_1-C_6))- or a

substituted or unsubstituted phenyl group;

Z^{102} is hydrogen; a substituted or unsubstituted alkyl group; a substituted or unsubstituted cycloalkyl group; a substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted, saturated or unsaturated heterocyclic group; or a substituted or unsubstituted, saturated or unsaturated heterobicyclic group; wherein said substituted alkyl, substituted cycloalkyl, substituted cycloalkenyl, substituted heterocyclic and substituted heterobicyclic group having one or more substituents each independently selected from the group consisting of hydroxyl, cyano, nitro, halo, substituted or unsubstituted (C_1-C_6), substituted or unsubstituted aryl, substituted or unsubstituted -C(O)-alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted -N(R)-(C_1-C_6) -OR, substituted or unsubstituted –N((C_1-C_6) -$OR)_2$,substituted or unsubstituted -N(R)-(C_1-C_6) -$C(O)_2R$, substituted or unsubstituted –(C_1-C_6) -N(R)-(C_1-C_6) -OR, substituted or unsubstituted –(C_1-C_6) -N(R)-(C_1-C_6) -$N(R)_2$, substituted or unsubstituted –(C_1-C_6) -C(O)N(R)-(C_1-C_6) -$N(R)_2$, substituted or unsubstituted sulfonamido, substituted or unsubstituted ureido, substituted or unsubstituted carboxamido, substituted or unsubstituted amino, substituted or unsubstituted –N(R)-(C_1-C_6) -OR, oxo, and a saturated, unsaturated or aromatic, substituted or unsubstituted heterocyclic group comprising one or more heteroatoms selected from the group consisting of N, O, and S; wherein the nitrogen atoms of said heterocyclic group or heterobicyclic group are independently optionally substituted by oxo, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted -$C(O)N(R)_2$, substituted or unsubstituted -C(O)-(C_1-C_6)-$N(R)_2$, -C(O)-alkyl, -C(O)-aryl, -C(O)-heteroaryl, substituted or unsubstituted arylalkyl group, or substituted or unsubstituted heteroarylalkyl; or

R_2 is a group of the formula -B-E, wherein B is a substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted azacycloalkyl,

substituted or unsubstituted amino, substituted or unsubstituted aminoalkylsulfonyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aminoalkylcarbonyl, substituted or unsubstituted alkylene, substituted or unsubstituted aminoalkyl, substituted or unsubstituted alkylenecarbonyl or substituted or unsubstituted aminoalkylcarbonyl group; and E is substituted or unsubstituted alkyl, a substituted or unsubstituted cycloalkyl, substituted or unsubstituted azacycloalkyl, a substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted (C_1-C_6)-azacycloalkyl-, substituted or unsubstituted azacycloalkylcarbonyl, substituted or unsubstituted azacycloalkylsulfonyl, substituted or unsubstituted azacycloalkylalkyl, substituted or unsubstituted heteroaryl-N(R)-(C_1-C_6)-, substituted or unsubstituted aryl-N(R)-(C_1-C_6)-, substituted or unsubstituted alkyl-N(R)-(C_1-C_6)-, substituted or unsubstituted heteroaryl-(C_1-C_6)-N(R)-, substituted or unsubstituted aryl-(C_1-C_6)-N(R)-, substituted or unsubstituted alkyl-(C_1-C_6)-N(R)-, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylcarbonyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted arylcarbonyl, substituted or unsubstituted heteroarylsulfonyl, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted arylsulfonyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted azacycloalkylcarbonylamino, substituted or unsubstituted heteroarylcarbonylamino, substituted or unsubstituted arylcarbonylamino, substituted or unsubstituted alkylcarbonylamino or substituted or unsubstituted aryl;

a is 1 and D_1, G_1, J_1, L_1 and M_1 are each independently selected from the group consisting of CR_a and N, provided that at least two of D_1, G_1, J_1, L_1 and M_1 are CR_a; or

a is 0, and one of D_1, G_1, L_1 and M_1 is NR_a, one of D_1, G_1, L_1 and M_1 is CR_a and the remainder are independently selected from the group consisting of CR_a and N, wherein R_a is as defined above;

b is 1 and D_2, G_2, J_2, L_2 and M_2 are each independently selected from the group consisting of CR_a and N, provided that at least two of D_2, G_2, J_2, L_2 and M_2 are CR_a; or

b is 0, and one of D_2, G_2, L_2 and M_2 is NR_a, one of D_2, G_2, L_2 and M_2 is CR_a and the remainder are independently selected from the group consisting of CR_a and N, wherein R_a is as defined above; and

n for each occurrence is independently an integer from 0 to 6;

provided that when A is –N(R)-, Z^{110} and Z^{111} are each a covalent bond, and R_2 is a 3,4-dihydroxytetrahydrofur-2-yl or a 3,4-diacyloxytetrahydrofur-2-yl, then Z^{100} is not alkyl, tetrahydropyranyl, tetrahydrofuranyl, piperidinyl or pyrrolidinyl;

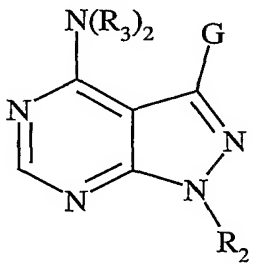
provided that when Z^{110} and Z^{111} are each a covalent bond, and R_2 is a 3,4-dihydroxytetrahydrofur-2-yl or a 3,4-diacyloxytetrahydrofur-2-yl, Z^{100} is a substituted or unsubstituted alkyl, then A is not alkyl, -O-, -C(O)-, -NHC(O)- or –C(O)O-;

provided that when Z^{110}-A-Z^{111} taken together are a covalent bond, then Z^{100} is not alkyl;

provided that when Z^{110}-A-Z^{111} taken together are a C_1-C_6 alkyl, then Z^{100} is not phenyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, furyl or thienyl; and

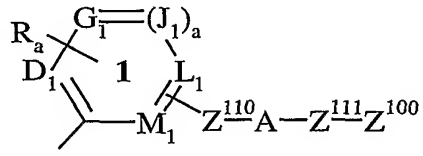
provided that when R_2 is a substituted or unsubstituted cyclopentyl, Z^{100} is an substituted or unsubstituted alkyl, Z^{110} and Z^{111} are each a covalent bond, then A is not –O-, -C(O)O-, or –N(R)-.

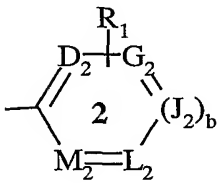
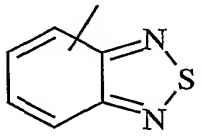
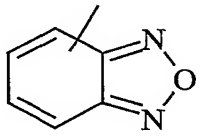
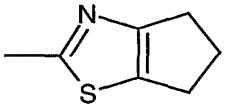
108. A compound of Formula (I)



(I)

racemic-diastereomeric mixtures, optical isomers, pharmaceutically-acceptable salts, prodrugs or biologically active metabolites thereof wherein:

G is 

where Z^{100} is  or a group optionally substituted with R_1 selected from the group consisting of alkyl, cycloalkyl, pyrrolidinyl, quinolinyl, quinoxalinyl, quinazolinyl, isoquinolinyl, phthalazinyl, imidazo[1,2-a]pyrimidinyl, 1H-imidazo[1,2-a]imidazolyl, imidazo[2,1-b][1,3]thiazolyl, naphthyl, tetrahydronaphthyl, benzothienyl, furanyl, thienyl, benzoxazolyl, benzoisoxazolyl, benzothiazolyl,  ,  ,  , thiazolyl, benzofuranyl, 2,3-dihydrobenzofuranyl, indolyl, isoxazolyl, tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, pyrazolyl, pyrrolyl, pyrrolopyridinyl, H-pyridinone, oxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, indolinyl, indazolyl, imidazo[1,2-a]pyridinyl, benzoisothiazolyl, 1,1-dioxybenzoisothiazolyl, pyrido-oxazolyl, pyrido-thiazolyl, pyrimido-oxazolyl, pyrimido-thiazolyl and benzimidazolyl;

Z^{110} is a covalent bond, or an optionally substituted (C_1-C_6) which is optionally substituted with one or more substituents selected from the group consisting of alkyl, CN, OH, halogen, NO_2, COOH, substituted

or unsubstituted amino and substituted or unsubstituted phenyl;

Z^{111} is a covalent bond, an optionally substituted (C_1-C_6) or an optionally substituted -$(CH_2)_n$-cycloalkyl-$(CH_2)_n$-; where the optionally substituted groups are optionally substituted with one or more substituents selected from the group consisting of alkyl, CN, OH, halogen, NO_2, COOH, substituted or unsubstituted amino and substituted or unsubstituted phenyl;

R_a and R_1 each represent one or more substituents for each occurrence independently selected from the group consisting of hydrogen, halogen, -CN, -NO_2, -C(O)OH, -C(O)H, -OH, -C(O)O-alkyl, -C(O)O-aryl, -C(O)O-heteroaryl, -C(O)-alkyl, -C(O)-aryl, -C(O)-heteroaryl, substituted or unsubstituted carboxamido, tetrazolyl, trifluoromethylcarbonylamino, trifluoromethylsulfonamido, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryloxy, substituted or unsubstituted heteroaryloxy, substituted or unsubstituted heteroarylalkoxy, substituted or unsubstituted arylalkoxy, substituted or unsubstituted alkyl-$S(O)_p$-, substituted or unsubstituted alkyl-S-, substituted or unsubstituted aryl-$S(O)_p$-, substituted or unsubstituted heteroaryl-$S(O)_p$-, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted alkynyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted amido groups, substituted or unsubstituted heteroarylthio, substituted or unsubstituted arylthio, -Z^{105}-C(O)N$(R)_2$, -Z^{105}-N(R)-C(O)-Z^{200}, -Z^{105}-N(R)-$S(O)_2$-Z^{200}, -Z^{105}-N(R)-C(O)-N(R)-Z^{200}, R_c and CH_2OR_c;

where R_c for each occurrence is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, -CH_2-NR_dR_e, -W-$(CH_2)_t$-NR_dR_e, -W-$(CH_2)_t$-O-alkyl, -W-$(CH_2)_t$-S-alkyl, or -W-$(CH_2)_t$-OH;

Z^{105} for each occurrence is independently a covalent bond or (C_1-C_6);

Z^{200} for each occurrence is independently a substituted or unsubstituted (C_1-C_6), substituted or unsubstituted phenyl or substituted or unsubstituted -(C_1-C_6)-phenyl;

R_d and R_e for each occurrence are independently H, alkyl, alkanoyl or SO_2-alkyl; or R_d, R_e and the nitrogen atom to which they are attached together form a five- or six-membered heterocyclic ring;

t for each occurrence is independently an integer from 2 to 6;

W for each occurrence is independently a direct bond or O, S, S(O), $S(O)_2$, or NR_f, wherein R_f for each occurrence is independently H or alkyl; or

R_1 is a substituted or unsubstituted carbocyclic or heterocyclic ring fused with ring 2;

R_3 for each occurrence is, independently, hydrogen, hydroxy, substituted or unsubstituted alkyl, substituted or unsubstituted -C(O)-alkyl, a substituted or unsubstituted -C(O)-aryl, or a substituted or unsubstituted –C(O)-heteroaryl or substituted or unsubstituted alkoxy;

A is –(C_1-C_6)-;

R for each occurrence is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl or substituted or unsubstituted aryl;

p is 1 or 2;

R_2 is H or a group of the formula -Z^{101}-Z^{102};

Z^{101} is a covalent bond, -(C_1-C_6)-, -(C_1-C_6)- -O-, -(C_1-C_6)- -C(O)-, -(C_1-C_6)- -C(O)O-, -(C_1-C_6)-C(O)-NH-, -(C_1-C_6)-C(O)-N((C_1-C_6))- or a substituted or unsubstituted phenyl group;

Z^{102} is hydrogen; a substituted or unsubstituted alkyl group; a substituted or unsubstituted cycloalkyl group; a substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted, saturated or unsaturated heterocyclic group; or a substituted or unsubstituted, saturated or unsaturated heterobicyclic group; wherein said substituted alkyl, substituted cycloalkyl, substituted cycloalkenyl, substituted heterocyclic and substituted heterobicyclic group having one or more substituents each independently selected from the group consisting of

hydroxyl, cyano, nitro, halo, substituted or unsubstituted (C_1-C_6), substituted or unsubstituted aryl, substituted or unsubstituted -C(O)-alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted -N(R)-(C_1-C_6) -OR, substituted or unsubstituted –N((C_1-C_6) -$OR)_2$,substituted or unsubstituted -N(R)-(C_1-C_6) -$C(O)_2$R, substituted or unsubstituted –(C_1-C_6) -N(R)-(C_1-C_6) -OR, substituted or unsubstituted –(C_1-C_6) -N(R)-(C_1-C_6) -$N(R)_2$, substituted or unsubstituted –(C_1-C_6) -C(O)N(R)-(C_1-C_6) -$N(R)_2$, substituted or unsubstituted sulfonamido, substituted or unsubstituted ureido, substituted or unsubstituted carboxamido, substituted or unsubstituted amino, substituted or unsubstituted –N(R)-(C_1-C_6) -OR, oxo, and a saturated, unsaturated or aromatic, substituted or unsubstituted heterocyclic group comprising one or more heteroatoms selected from the group consisting of N, O, and S; wherein the nitrogen atoms of said heterocyclic group or heterobicyclic group are independently optionally substituted by oxo, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted -C(O)$N(R)_2$, substituted or unsubstituted -C(O)-(C_1-C_6)-$N(R)_2$, -C(O)-alkyl, -C(O)-aryl, -C(O)-heteroaryl, substituted or unsubstituted arylalkyl group, or substituted or unsubstituted heteroarylalkyl; or

R_2 is a group of the formula -B-E, wherein B is a substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted azacycloalkyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkylsulfonyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aminoalkylcarbonyl, substituted or unsubstituted alkylene, substituted or unsubstituted aminoalkyl, substituted or unsubstituted alkylenecarbonyl or substituted or unsubstituted aminoalkylcarbonyl group; and E is substituted or unsubstituted alkyl, a substituted or unsubstituted cycloalkyl, substituted or unsubstituted azacycloalkyl, a substituted or unsubstituted heterocycloalkyl, substituted or

unsubstituted (C_1-C_6)-azacycloalkyl-, substituted or unsubstituted azacycloalkylcarbonyl, substituted or unsubstituted azacycloalkylsulfonyl, substituted or unsubstituted azacycloalkylalkyl, substituted or unsubstituted heteroaryl-N(R)-(C_1-C_6)-, substituted or unsubstituted aryl-N(R)-(C_1-C_6)-, substituted or unsubstituted alkyl-N(R)-(C_1-C_6)-, substituted or unsubstituted heteroaryl-(C_1-C_6)-N(R)-, substituted or unsubstituted aryl-(C_1-C_6)-N(R)-, substituted or unsubstituted alkyl-(C_1-C_6)-N(R)-, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylcarbonyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted arylcarbonyl, substituted or unsubstituted heteroarylsulfonyl, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted arylsulfonyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted azacycloalkylcarbonylamino, substituted or unsubstituted heteroarylcarbonylamino, substituted or unsubstituted arylcarbonylamino, substituted or unsubstituted alkylcarbonylamino or substituted or unsubstituted aryl;

a is 1 and D_1, G_1, J_1, L_1 and M_1 are each independently selected from the group consisting of CR_a and N, provided that at least two of D_1, G_1, J_1, L_1 and M_1 are CR_a; or

a is 0, and one of D_1, G_1, L_1 and M_1 is NR_a, one of D_1, G_1, L_1 and M_1 is CR_a and the remainder are independently selected from the group consisting of CR_a and N, wherein R_a is as defined above;

b is 1 and D_2, G_2, J_2, L_2 and M_2 are each independently selected from the group consisting of CR_a and N, provided that at least two of D_2, G_2, J_2, L_2 and M_2 are CR_a; or

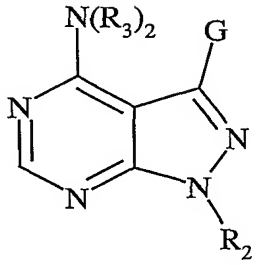
b is 0, and one of D_2, G_2, L_2 and M_2 is NR_a, one of D_2, G_2, L_2 and M_2 is CR_a and the remainder are independently selected from the group consisting of CR_a and N, wherein R_a is as defined above; and

n for each occurrence is independently an integer from 0 to 6;

provided that when Z^{110}-A-Z^{111} taken together are a C_1-C_6 alkyl, then Z^{100} is not phenyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl,

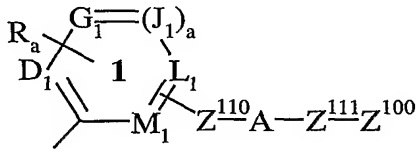
pyrazinyl, pyridazinyl, furyl or thienyl.

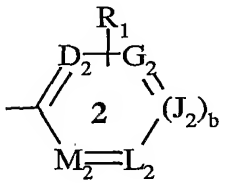
109. A compound of Formula (I)

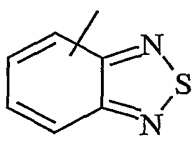
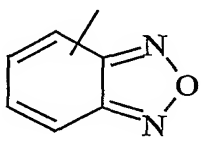


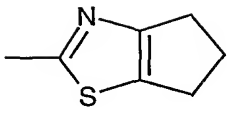
(I)

racemic-diastereomeric mixtures, optical isomers, pharmaceutically-acceptable salts, prodrugs or biologically active metabolites thereof wherein:

G is 

where Z^{100} is  or a group optionally substituted with R_1 selected from the group consisting of pyrrolidinyl, quinolinyl, quinoxalinyl, quinazolinyl, isoquinolinyl, phthalazinyl, imidazo[1,2-a]pyrimidinyl, 1H-imidazo[1,2-a]imidazolyl, imidazo[2,1-b][1,3]thiazolyl, naphthyl, tetrahydronaphthyl, benzothienyl, furanyl, thienyl, benzoxazolyl, benzoisoxazolyl, benzothiazolyl,

 ,  ,



, thiazolyl, benzofuranyl, 2,3-dihydrobenzofuranyl, indolyl, isoxazolyl, tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, pyrazolyl, pyrrolyl, pyrrolopyridinyl, H-pyridinone, oxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, indolinyl, indazolyl, imidazo[1,2-a]pyridinyl, benzoisothiazolyl, 1,1-dioxybenzoisothiazolyl, pyrido-oxazolyl, pyrido-thiazolyl, pyrimido-oxazolyl, pyrimido-thiazolyl and benzimidazolyl;

R_a and R_1 each represent one or more substituents for each occurrence independently selected from the group consisting of hydrogen, halogen, -CN, -NO_2, -C(O)OH, -C(O)H, -OH, -C(O)O-alkyl, -C(O)O-aryl, -C(O)O-heteroaryl, -C(O)-alkyl, -C(O)-aryl, -C(O)-heteroaryl, substituted or unsubstituted carboxamido, tetrazolyl, trifluoromethylcarbonylamino, trifluoromethylsulfonamido, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryloxy, substituted or unsubstituted heteroaryloxy, substituted or unsubstituted heteroarylalkoxy, substituted or unsubstituted arylalkoxy, substituted or unsubstituted alkyl-$S(O)_p$-, substituted or unsubstituted alkyl-S-, substituted or unsubstituted aryl-$S(O)_p$-, substituted or unsubstituted heteroaryl-$S(O)_p$-, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted alkynyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted amido groups, substituted or unsubstituted heteroarylthio, substituted or unsubstituted arylthio, -Z^{105}-C(O)N$(R)_2$, -Z^{105}-N(R)-C(O)-Z^{200}, -Z^{105}-N(R)-S$(O)_2$-Z^{200}, -Z^{105}-N(R)-C(O)-N(R)-Z^{200}, R_c and CH_2OR_c;

where R_c for each occurrence is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, -CH_2-NR_dR_e, -

W-$(CH_2)_t$-NR_dR_e, -W-$(CH_2)_t$-O-alkyl, -W-$(CH_2)_t$-S-alkyl, or -W-$(CH_2)_t$-OH;

Z^{105} for each occurrence is independently a covalent bond or (C_1-C_6);

Z^{200} for each occurrence is independently a substituted or unsubstituted (C_1-C_6), substituted or unsubstituted phenyl or substituted or unsubstituted -(C_1-C_6)-phenyl;

R_d and R_e for each occurrence are independently H, alkyl, alkanoyl or SO_2-alkyl; or R_d, R_e and the nitrogen atom to which they are attached together form a five- or six-membered heterocyclic ring;

t for each occurrence is independently an integer from 2 to 6;

W for each occurrence is independently a direct bond or O, S, S(O), $S(O)_2$, or NR_f, wherein R_f for each occurrence is independently H or alkyl; or

R_1 is a substituted or unsubstituted carbocyclic or heterocyclic ring fused with ring 2;

R_3 for each occurrence is, independently, hydrogen, hydroxy, substituted or unsubstituted alkyl, substituted or unsubstituted -C(O)-alkyl, a substituted or unsubstituted -C(O)-aryl, or a substituted or unsubstituted –C(O)-heteroaryl or substituted or unsubstituted alkoxy;

R for each occurrence is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl or substituted or unsubstituted aryl;

p is 1 or 2;

Z^{110}-A-Z^{111} taken together is a covalent bond; and

R_2 is H or a group of the formula -Z^{101}-Z^{102};

Z^{101} is a covalent bond, -(C_1-C_6)-, -(C_1-C_6)- -O-, -(C_1-C_6)- -C(O)-, -(C_1-C_6)- -C(O)O-, -(C_1-C_6)-C(O)-NH-, -(C_1-C_6)-C(O)-N((C_1-C_6))- or a substituted or unsubstituted phenyl group;

Z^{102} is hydrogen; a substituted or unsubstituted alkyl group; a substituted or unsubstituted cycloalkyl group; a substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted, saturated or unsaturated heterocyclic group; or a substituted or unsubstituted, saturated or unsaturated heterobicyclic group; wherein said substituted alkyl, substituted cycloalkyl, substituted cycloalkenyl, substituted

heterocyclic and substituted heterobicyclic group having one or more substituents each independently selected from the group consisting of hydroxyl, cyano, nitro, halo, substituted or unsubstituted (C_1-C_6), substituted or unsubstituted aryl, substituted or unsubstituted -C(O)-alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted -N(R)-(C_1-C_6) -OR, substituted or unsubstituted –N((C_1-C_6) -OR)$_2$,substituted or unsubstituted -N(R)-(C_1-C_6) -C(O)$_2$R, substituted or unsubstituted –(C_1-C_6) -N(R)-(C_1-C_6) -OR, substituted or unsubstituted –(C_1-C_6) -N(R)-(C_1-C_6) -N(R)$_2$, substituted or unsubstituted –(C_1-C_6) -C(O)N(R)-(C_1-C_6) -N(R)$_2$, substituted or unsubstituted sulfonamido, substituted or unsubstituted ureido, substituted or unsubstituted carboxamido, substituted or unsubstituted amino, substituted or unsubstituted –N(R)-(C_1-C_6) -OR, oxo, and a saturated, unsaturated or aromatic, substituted or unsubstituted heterocyclic group comprising one or more heteroatoms selected from the group consisting of N, O, and S; wherein the nitrogen atoms of said heterocyclic group or heterobicyclic group are independently optionally substituted by oxo, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted -C(O)N(R)$_2$, substituted or unsubstituted -C(O)-(C_1-C_6)-N(R)$_2$, -C(O)-alkyl, -C(O)-aryl, -C(O)-heteroaryl, substituted or unsubstituted arylalkyl group, or substituted or unsubstituted heteroarylalkyl; or

R_2 is a group of the formula -B-E, wherein B is a substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted azacycloalkyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkylsulfonyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aminoalkylcarbonyl, substituted or unsubstituted alkylene, substituted or unsubstituted aminoalkyl, substituted or unsubstituted alkylenecarbonyl or substituted or unsubstituted aminoalkylcarbonyl group; and E is substituted or unsubstituted alkyl, a substituted or

unsubstituted cycloalkyl, substituted or unsubstituted azacycloalkyl, a substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted (C_1-C_6)-azacycloalkyl-, substituted or unsubstituted azacycloalkylcarbonyl, substituted or unsubstituted azacycloalkylsulfonyl, substituted or unsubstituted azacycloalkylalkyl, substituted or unsubstituted heteroaryl-N(R)-(C_1-C_6)-, substituted or unsubstituted aryl-N(R)-(C_1-C_6)-, substituted or unsubstituted alkyl-N(R)-(C_1-C_6)-, substituted or unsubstituted heteroaryl-(C_1-C_6)-N(R)-, substituted or unsubstituted aryl-(C_1-C_6)-N(R)-, substituted or unsubstituted alkyl-(C_1-C_6)-N(R)-, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylcarbonyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted arylcarbonyl, substituted or unsubstituted heteroarylsulfonyl, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted arylsulfonyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted azacycloalkylcarbonylamino, substituted or unsubstituted heteroarylcarbonylamino, substituted or unsubstituted arylcarbonylamino, substituted or unsubstituted alkylcarbonylamino or substituted or unsubstituted aryl;

a is 1 and D_1, G_1, J_1, L_1 and M_1 are each independently selected from the group consisting of CR_a and N, provided that at least two of D_1, G_1, J_1, L_1 and M_1 are CR_a; or

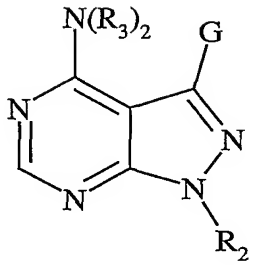
a is 0, and one of D_1, G_1, L_1 and M_1 is NR_a, one of D_1, G_1, L_1 and M_1 is CR_a and the remainder are independently selected from the group consisting of CR_a and N, wherein R_a is as defined above;

b is 1 and D_2, G_2, J_2, L_2 and M_2 are each independently selected from the group consisting of CR_a and N, provided that at least two of D_2, G_2, J_2, L_2 and M_2 are CR_a; or

b is 0, and one of D_2, G_2, L_2 and M_2 is NR_a, one of D_2, G_2, L_2 and M_2 is CR_a and the remainder are independently selected from the group consisting of CR_a and N, wherein R_a is as defined above; and

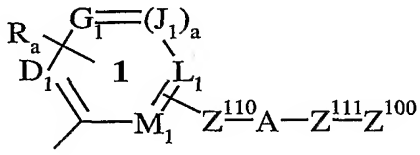
n for each occurrence is independently an integer from 0 to 6.

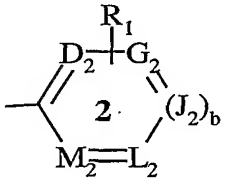
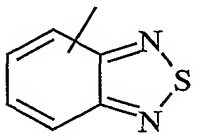
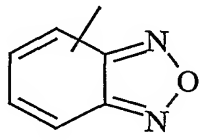
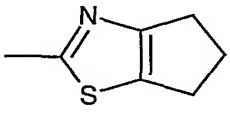
110. A compound of Formula (I)



(I)

racemic-diastereomeric mixtures, optical isomers, pharmaceutically-acceptable salts, prodrugs or biologically active metabolites thereof wherein:

G is 

where Z^{100} is  or a group optionally substituted with R_1 selected from the group consisting of alkyl, cycloalkyl, pyrrolidinyl, quinolinyl, quinoxalinyl, quinazolinyl, isoquinolinyl, phthalazinyl, imidazo[1,2-a]pyrimidinyl, 1H-imidazo[1,2-a]imidazolyl, imidazo[2,1-b][1,3]thiazolyl, naphthyl, tetrahydronaphthyl, benzothienyl, furanyl, thienyl, benzoxazolyl, benzoisoxazolyl, benzothiazolyl,  ,  ,  , thiazolyl, benzofuranyl, 2,3-

dihydrobenzofuranyl, indolyl, isoxazolyl, tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, pyrazolyl, pyrrolyl, pyrrolopyridinyl, H-pyridinone, oxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, indolinyl, indazolyl, imidazo[1,2-a]pyridinyl, benzoisothiazolyl, 1,1-dioxybenzoisothiazolyl, pyrido-oxazolyl, pyrido-thiazolyl, pyrimido-oxazolyl, pyrimido-thiazolyl and benzimidazolyl;

Z^{110} is a covalent bond, or an optionally substituted (C_1-C_6) which is optionally substituted with one or more substituents selected from the group consisting of alkyl, CN, OH, halogen, NO_2, COOH, substituted or unsubstituted amino and substituted or unsubstituted phenyl;

Z^{111} is a covalent bond, an optionally substituted (C_1-C_6) or an optionally substituted -$(CH_2)_n$-cycloalkyl-$(CH_2)_n$-; where the optionally substituted groups are optionally substituted with one or more substituents selected from the group consisting of alkyl, CN, OH, halogen, NO_2, COOH, substituted or unsubstituted amino and substituted or unsubstituted phenyl;

R_a and R_1 each represent one or more substituents for each occurrence independently selected from the group consisting of hydrogen, halogen, -CN, -NO_2, -C(O)OH, -C(O)H, -OH, -C(O)O-alkyl, -C(O)O-aryl, -C(O)O-heteroaryl, -C(O)-alkyl, -C(O)-aryl, -C(O)-heteroaryl, substituted or unsubstituted carboxamido, tetrazolyl, trifluoromethylcarbonylamino, trifluoromethylsulfonamido, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryloxy, substituted or unsubstituted heteroaryloxy, substituted or unsubstituted heteroarylalkoxy, substituted or unsubstituted arylalkoxy, substituted or unsubstituted alkyl-$S(O)_p$-, substituted or unsubstituted alkyl-S-, substituted or unsubstituted aryl-$S(O)_p$-, substituted or unsubstituted heteroaryl-$S(O)_p$-, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or

unsubstituted alkynyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted amido groups, substituted or unsubstituted heteroarylthio, substituted or unsubstituted arylthio, $-Z^{105}-C(O)N(R)_2$, $-Z^{105}-N(R)-C(O)-Z^{200}$, $-Z^{105}-N(R)-S(O)_2-Z^{200}$, $-Z^{105}-N(R)-C(O)-N(R)-Z^{200}$, R_c and CH_2OR_c;

where R_c for each occurrence is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, $-CH_2-NR_dR_e$, $-W-(CH_2)_t-NR_dR_e$, $-W-(CH_2)_t-O$-alkyl, $-W-(CH_2)_t-S$-alkyl, or $-W-(CH_2)_t-OH$;

Z^{105} for each occurrence is independently a covalent bond or (C_1-C_6);

Z^{200} for each occurrence is independently a substituted or unsubstituted (C_1-C_6), substituted or unsubstituted phenyl or substituted or unsubstituted $-(C_1-C_6)$-phenyl;

R_d and R_e for each occurrence are independently H, alkyl, alkanoyl or SO_2-alkyl; or R_d, R_e and the nitrogen atom to which they are attached together form a five- or six-membered heterocyclic ring;

t for each occurrence is independently an integer from 2 to 6;

W for each occurrence is independently a direct bond or O, S, S(O), $S(O)_2$, or NR_f, wherein R_f for each occurrence is independently H or alkyl; or

R_1 is a substituted or unsubstituted carbocyclic or heterocyclic ring fused with ring 2;

R_3 for each occurrence is, independently, substituted or unsubstituted -C(O)-alkyl, a substituted or unsubstituted -C(O)-aryl, or a substituted or unsubstituted –C(O)-heteroaryl.

A is $-(C_1-C_6)$ -, -O-; -S-; $-S(O)_p-$; -N(R)-; -N(C(O)OR)-; -N(C(O)R)-; $-N(SO_2R)-$; $-CH_2O-$; $-CH_2S-$; $-CH_2N(R)-$; -CH(NR)-; $-CH_2N(C(O)R))-$; $-CH_2N(C(O)OR)-$; $-CH_2N(SO_2R)-$; -CH(NHR)-; -CH(NHC(O)R)-; $-CH(NHSO_2R)-$; -CH(NHC(O)OR)-; -CH(OC(O)R)-; -CH(OC(O)NHR)-; -CH=CH-; -C(=NOR)-; -C(O)-; -CH(OR)-; -C(O)N(R)-; -N(R)C(O)-; $-N(R)S(O)_p-$; -OC(O)N(R)-; ; $-N(R)-C(O)-(CH_2)_n-N(R)-$, -N(R)C(O)O-; $-N(R)-(CH_2)_{n+1}-C(O)-$, $-S(O)_pN(R)-$; $-O-(CR_2)_{n+1}-C(O)-$, $-O-(CR_2)_{n+1}-O-$, $-N(C(O)R)S(O)_p-$; $-N(R)S(O)_pN(R)-$; $-N(R)-C(O)-(CH_2)_n-O-$, -C(O)N(R)C(O)-; -

$S(O)_pN(R)C(O)$-; -$OS(O)_pN(R)$-; -$N(R)S(O)_pO$-; -$N(R)S(O)_pC(O)$-; -$SO_pN(C(O)R)$-; -$N(R)SO_pN(R)$-; -C(O)O-; -$N(R)P(OR_b)O$-; -$N(R)P(OR_b)$-; -$N(R)P(O)(OR_b)O$-; -$N(R)P(O)(OR_b)$-; -$N(C(O)R)P(OR_b)O$-; -$N(C(O)R)P(OR_b)$-; -$N(C(O)R)P(O)(OR_b)O$-, or -$N(C(O)R)P(OR_b)$-;

where R for each occurrence is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl or substituted or unsubstituted aryl;

R_b for each occurrence is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl or substituted or unsubstituted aryl;

p is 1 or 2; or

in a phosphorus containing group, the nitrogen atom, the phosphorus atom, R and R_b together form a five- or six-membered heterocyclic ring; or

A is $NRSO_2$ and R, R_a and the nitrogen atom together form a substituted or unsubstituted five or-six-membered heterocyclic ring fused to ring 1; or

Z^{110}-A-Z^{111} taken together is a covalent bond; and

R_2 is H or a group of the formula -Z^{101}-Z^{102};

Z^{101} is a covalent bond, -(C_1-C_6)-, -(C_1-C_6)- -O-, -(C_1-C_6)- -C(O)-, -(C_1-C_6)- -C(O)O-, -(C_1-C_6)-C(O)-NH-, -(C_1-C_6)-C(O)-N((C_1-C_6))- or a substituted or unsubstituted phenyl group;

Z^{102} is hydrogen; a substituted or unsubstituted alkyl group; a substituted or unsubstituted cycloalkyl group; a substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted, saturated or unsaturated heterocyclic group; or a substituted or unsubstituted, saturated or unsaturated heterobicyclic group; wherein said substituted alkyl, substituted cycloalkyl, substituted cycloalkenyl, substituted heterocyclic and substituted heterobicyclic group having one or more substituents each independently selected from the group consisting of hydroxyl, cyano, nitro, halo, substituted or unsubstituted (C_1-C_6), substituted or unsubstituted aryl, substituted or unsubstituted -C(O)-alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted -N(R)-(C_1-C_6) -OR, substituted or unsubstituted –N((C_1-C_6) -

$OR)_2$,substituted or unsubstituted -N(R)-(C_1-C_6) -$C(O)_2$R, substituted or unsubstituted –(C_1-C_6) -N(R)-(C_1-C_6) -OR, substituted or unsubstituted –(C_1-C_6) -N(R)-(C_1-C_6) -$N(R)_2$, substituted or unsubstituted –(C_1-C_6) -C(O)N(R)-(C_1-C_6) -$N(R)_2$, substituted or unsubstituted sulfonamido, substituted or unsubstituted ureido, substituted or unsubstituted carboxamido, substituted or unsubstituted amino, substituted or unsubstituted –N(R)-(C_1-C_6) -OR, oxo, and a saturated, unsaturated or aromatic, substituted or unsubstituted heterocyclic group comprising one or more heteroatoms selected from the group consisting of N, O, and S; wherein the nitrogen atoms of said heterocyclic group or heterobicyclic group are independently optionally substituted by oxo, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted -C(O)$N(R)_2$, substituted or unsubstituted -C(O)-(C_1-C_6)-$N(R)_2$, -C(O)-alkyl, -C(O)-aryl, -C(O)-heteroaryl, substituted or unsubstituted arylalkyl group, or substituted or unsubstituted heteroarylalkyl; or

R_2 is a group of the formula -B-E, wherein B is a substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted azacycloalkyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkylsulfonyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aminoalkylcarbonyl, substituted or unsubstituted alkylene, substituted or unsubstituted aminoalkyl, substituted or unsubstituted alkylenecarbonyl or substituted or unsubstituted aminoalkylcarbonyl group; and E is substituted or unsubstituted alkyl, a substituted or unsubstituted cycloalkyl, substituted or unsubstituted azacycloalkyl, a substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted (C_1-C_6)-azacycloalkyl-, substituted or unsubstituted azacycloalkylcarbonyl, substituted or unsubstituted azacycloalkylsulfonyl, substituted or unsubstituted azacycloalkylalkyl, substituted or unsubstituted heteroaryl-N(R)-(C_1-

C_6)-, substituted or unsubstituted aryl-N(R)-(C_1-C_6)-, substituted or unsubstituted alkyl-N(R)-(C_1-C_6)-, substituted or unsubstituted heteroaryl-(C_1-C_6)-N(R)-, substituted or unsubstituted aryl-(C_1-C_6)-N(R)-, substituted or unsubstituted alkyl-(C_1-C_6)-N(R)-, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylcarbonyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted arylcarbonyl, substituted or unsubstituted heteroarylsulfonyl, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted arylsulfonyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted azacycloalkylcarbonylamino, substituted or unsubstituted heteroarylcarbonylamino, substituted or unsubstituted arylcarbonylamino, substituted or unsubstituted alkylcarbonylamino or substituted or unsubstituted aryl;

a is 1 and D_1, G_1, J_1, L_1 and M_1 are each independently selected from the group consisting of CR_a and N, provided that at least two of D_1, G_1, J_1, L_1 and M_1 are CR_a; or

a is 0, and one of D_1, G_1, L_1 and M_1 is NR_a, one of D_1, G_1, L_1 and M_1 is CR_a and the remainder are independently selected from the group consisting of CR_a and N, wherein R_a is as defined above;

b is 1 and D_2, G_2, J_2, L_2 and M_2 are each independently selected from the group consisting of CR_a and N, provided that at least two of D_2, G_2, J_2, L_2 and M_2 are CR_a; or

b is 0, and one of D_2, G_2, L_2 and M_2 is NR_a, one of D_2, G_2, L_2 and M_2 is CR_a and the remainder are independently selected from the group consisting of CR_a and N, wherein R_a is as defined above; and

n for each occurrence is independently an integer from 0 to 6;

provided that when A is –N(R)-, Z^{110} and Z^{111} are each a covalent bond, and R_2 is a 3,4-dihydroxytetrahydrofur-2-yl or a 3,4-diacyloxytetrahydrofur-2-yl, then Z^{100} is not alkyl, tetrahydropyranyl, tetrahydrofuranyl, piperidinyl or pyrrolidinyl;

provided that when Z^{110} and Z^{111} are each a covalent bond, and R_2 is a 3,4-dihydroxytetrahydrofur-2-yl or a 3,4-diacyloxytetrahydrofur-2-yl, Z^{100}

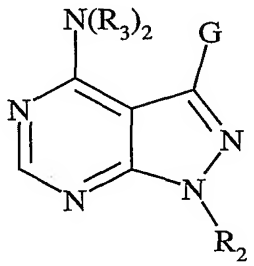
is a substituted or unsubstituted alkyl, then A is not alkyl, -O-, -C(O)-, -NHC(O)- or –C(O)O-;

provided that when Z^{110}-A-Z^{111} taken together are a covalent bond, then Z^{100} is not alkyl;

provided that when Z^{110}-A-Z^{111} taken together are a C_1-C_6 alkyl, then Z^{100} is not phenyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, furyl or thienyl; and

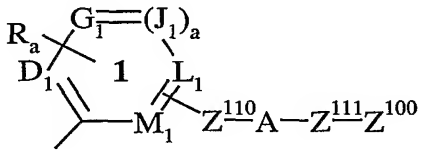
provided that when R_2 is a substituted or unsubstituted cyclopentyl, Z^{100} is an substituted or unsubstituted alkyl, Z^{110} and Z^{111} are each a covalent bond, then A is not –O-, -C(O)O-, or –N(R)-.

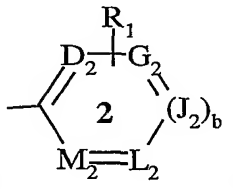
111. A compound of Formula (I)

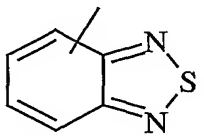
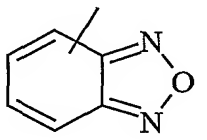
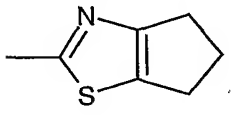


(I)

racemic-diastereomeric mixtures, optical isomers, pharmaceutically-acceptable salts, prodrugs or biologically active metabolites thereof wherein:

G is 

where Z^{100} is  or a group optionally substituted with R_1 selected from the group consisting of alkyl, cycloalkyl, pyrrolidinyl,

quinolinyl, quinoxalinyl, quinazolinyl, isoquinolinyl, phthalazinyl, imidazo[1,2-a]pyrimidinyl, 1H-imidazo[1,2-a]imidazolyl, imidazo[2,1-b][1,3]thiazolyl, naphthyl, tetrahydronaphthyl, benzothienyl, furanyl, thienyl, benzoxazolyl, benzoisoxazolyl, benzothiazolyl,  ,  ,  , thiazolyl, benzofuranyl, 2,3-dihydrobenzofuranyl, indolyl, isoxazolyl, tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, pyrazolyl, pyrrolyl, pyrrolopyridinyl, H-pyridinone, oxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, indolinyl, indazolyl, imidazo[1,2-a]pyridinyl, benzoisothiazolyl, 1,1-dioxybenzoisothiazolyl, pyrido-oxazolyl, pyrido-thiazolyl, pyrimido-oxazolyl, pyrimido-thiazolyl and benzimidazolyl;

Z^{110} is a covalent bond, or an optionally substituted (C_1-C_6) which is optionally substituted with one or more substituents selected from the group consisting of alkyl, CN, OH, halogen, NO_2, COOH, substituted or unsubstituted amino and substituted or unsubstituted phenyl;

Z^{111} is a covalent bond, an optionally substituted (C_1-C_6) or an optionally substituted -$(CH_2)_n$-cycloalkyl-$(CH_2)_n$-; where the optionally substituted groups are optionally substituted with one or more substituents selected from the group consisting of alkyl, CN, OH, halogen, NO_2, COOH, substituted or unsubstituted amino and substituted or unsubstituted phenyl;

R_a and R_1 each represent one or more substituents for each occurrence independently selected from the group consisting of hydrogen, halogen, -CN, -NO_2, -C(O)OH, -C(O)H, -OH, -C(O)O-alkyl, -C(O)O-aryl, -C(O)O-heteroaryl, -C(O)-alkyl, -C(O)-aryl, -C(O)-heteroaryl, substituted or unsubstituted carboxamido, tetrazolyl, trifluoromethylcarbonylamino, trifluoromethylsulfonamido, substituted or unsubstituted alkyl, substituted or unsubstituted

cycloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryloxy, substituted or unsubstituted heteroaryloxy, substituted or unsubstituted heteroarylalkoxy, substituted or unsubstituted arylalkoxy, substituted or unsubstituted alkyl-$S(O)_p$-, substituted or unsubstituted alkyl-S-, substituted or unsubstituted aryl-$S(O)_p$-, substituted or unsubstituted heteroaryl-$S(O)_p$-, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted alkynyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted amido groups, substituted or unsubstituted heteroarylthio, substituted or unsubstituted arylthio, $-Z^{105}-C(O)N(R)_2$, $-Z^{105}-N(R)-C(O)-Z^{200}$, $-Z^{105}-N(R)-S(O)_2-Z^{200}$, $-Z^{105}-N(R)-C(O)-N(R)-Z^{200}$, R_c and CH_2OR_c;

where R_c for each occurrence is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, $-CH_2-NR_dR_e$, $-W-(CH_2)_t-NR_dR_e$, $-W-(CH_2)_t-O$-alkyl, $-W-(CH_2)_t-S$-alkyl, or $-W-(CH_2)_t-OH$;

Z^{105} for each occurrence is independently a covalent bond or (C_1-C_6);

Z^{200} for each occurrence is independently a substituted or unsubstituted (C_1-C_6), substituted or unsubstituted phenyl or substituted or unsubstituted -(C_1-C_6)-phenyl;

R_d and R_e for each occurrence are independently H, alkyl, alkanoyl or SO_2-alkyl; or R_d, R_e and the nitrogen atom to which they are attached together form a five- or six-membered heterocyclic ring;

t for each occurrence is independently an integer from 2 to 6;

W for each occurrence is independently a direct bond or O, S, S(O), $S(O)_2$, or NR_f, wherein R_f for each occurrence is independently H or alkyl; or

R_1 is a substituted or unsubstituted carbocyclic or heterocyclic ring fused with ring 2;

R_3 for each occurrence is, independently, hydrogen, hydroxy, substituted or unsubstituted alkyl, substituted or unsubstituted -C(O)-alkyl, a

substituted or unsubstituted -C(O)-aryl, or a substituted or unsubstituted –C(O)-heteroaryl or substituted or unsubstituted alkoxy;

A is $-(C_1-C_6)$ -, -O-; -S-; $-S(O)_p$-; -N(R)-; -N(C(O)OR)-; -N(C(O)R)-; -N(SO_2R)-; $-CH_2O$-; $-CH_2S$-; $-CH_2N(R)$-; -CH(NR)-; $-CH_2N(C(O)R)$-; $-CH_2N(C(O)OR)$-; $-CH_2N(SO_2R)$-; -CH(NHR)-; -CH(NHC(O)R)-; -CH($NHSO_2$R)-; -CH(NHC(O)OR)-; -CH(OC(O)R)-; -CH(OC(O)NHR)-; -CH=CH-; -C(=NOR)-; -C(O)-; -CH(OR)-; -C(O)N(R)-; -N(R)C(O)-; $-N(R)S(O)_p$-; -OC(O)N(R)-; ; $-N(R)-C(O)-(CH_2)_n-N(R)$-, -N(R)C(O)O-; $-N(R)-(CH_2)_{n+1}-C(O)$-, $-S(O)_pN(R)$-; $-O-(CR_2)_{n+1}-C(O)$-, $-O-(CR_2)_{n+1}-O$-, $-N(C(O)R)S(O)_p$-; $-N(R)S(O)_pN(R)$-; $-N(R)-C(O)-(CH_2)_n-O$-, -C(O)N(R)C(O)-; $-S(O)_pN(R)C(O)$-; $-OS(O)_pN(R)$-; $-N(R)S(O)_pO$-; $-N(R)S(O)_pC(O)$-; $-SO_pN(C(O)R)$-; $-N(R)SO_pN(R)$-; -C(O)O-; $-N(R)P(OR_b)O$-; $-N(R)P(OR_b)$-; $-N(R)P(O)(OR_b)O$-; $-N(R)P(O)(OR_b)$-; $-N(C(O)R)P(OR_b)O$-; $-N(C(O)R)P(OR_b)$-; $-N(C(O)R)P(O)(OR_b)O$-, or $-N(C(O)R)P(OR_b)$-;

where R for each occurrence is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl or substituted or unsubstituted aryl;

R_b for each occurrence is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl or substituted or unsubstituted aryl;

p is 1 or 2; or

in a phosphorus containing group, the nitrogen atom, the phosphorus atom, R and R_b together form a five- or six-membered heterocyclic ring; or

A is $NRSO_2$ and R, R_a and the nitrogen atom together form a substituted or unsubstituted five or-six-membered heterocyclic ring fused to ring 1; or

Z^{110}-A-Z^{111} taken together is a covalent bond; and

R_2 is a group of the formula $-Z^{101}-Z^{102}$;

Z^{101} is a covalent bond, $-(C_1-C_6)$-, $-(C_1-C_6)$- -O-, $-(C_1-C_6)$- -C(O)-, $-(C_1-C_6)$- -C(O)O-, $-(C_1-C_6)$-C(O)-NH-, $-(C_1-C_6)$-C(O)-N((C_1-C_6))- or a substituted or unsubstituted phenyl group;

Z^{102} is a substituted or unsubstituted cycloalkenyl, wherein said substituted cycloalkenyl has one or more substituents each independently selected from the group consisting of hydroxyl, cyano, nitro, halo, substituted or unsubstituted (C_1-C_6), substituted or unsubstituted aryl, substituted or unsubstituted -C(O)-alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted -N(R)-(C_1-C_6) -OR, substituted or unsubstituted –N((C_1-C_6) -OR)$_2$, substituted or unsubstituted -N(R)-(C_1-C_6) -C(O)$_2$R, substituted or unsubstituted –(C_1-C_6) -N(R)-(C_1-C_6) -OR, substituted or unsubstituted –(C_1-C_6) -N(R)-(C_1-C_6) -N(R)$_2$, substituted or unsubstituted –(C_1-C_6) -C(O)N(R)-(C_1-C_6) -N(R)$_2$, substituted or unsubstituted sulfonamido, substituted or unsubstituted ureido, substituted or unsubstituted carboxamido, substituted or unsubstituted amino, substituted or unsubstituted –N(R)-(C_1-C_6) -OR, oxo, and a saturated, unsaturated or aromatic, substituted or unsubstituted heterocyclic group comprising one or more heteroatoms selected from the group consisting of N, O, and S; wherein the nitrogen atoms of said heterocyclic group or heterobicyclic group are independently optionally substituted by oxo, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted -C(O)N(R)$_2$, substituted or unsubstituted -C(O)-(C_1-C_6)-N(R)$_2$, -C(O)-alkyl, -C(O)-aryl, -C(O)-heteroaryl, substituted or unsubstituted arylalkyl group, or substituted or unsubstituted heteroarylalkyl;

a is 1 and D_1, G_1, J_1, L_1 and M_1 are each independently selected from the group consisting of CR_a and N, provided that at least two of D_1, G_1, J_1, L_1 and M_1 are CR_a; or

a is 0, and one of D_1, G_1, L_1 and M_1 is NR_a, one of D_1, G_1, L_1 and M_1 is CR_a and the remainder are independently selected from the group consisting of CR_a and N, wherein R_a is as defined above;

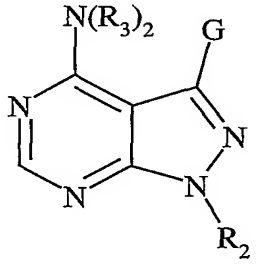
b is 1 and D_2, G_2, J_2, L_2 and M_2 are each independently selected from the group consisting of CR_a and N, provided that at least two of D_2, G_2, J_2, L_2 and M_2 are CR_a; or

b is 0, and one of D_2, G_2, L_2 and M_2 is NR_a, one of D_2, G_2, L_2 and M_2 is CR_a

and the remainder are independently selected from the group consisting of CR_a and N, wherein R_a is as defined above; and

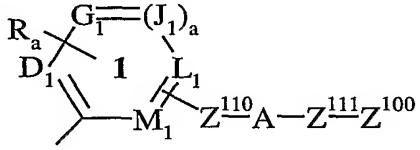
n for each occurrence is independently an integer from 0 to 6.

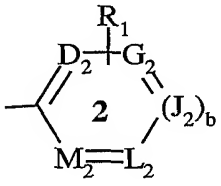
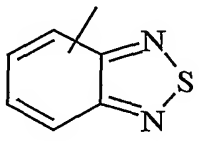
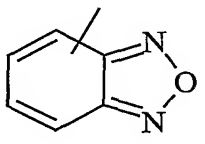
112. A compound of Formula (I)

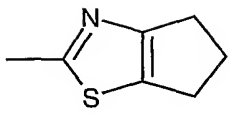


(I)

racemic-diastereomeric mixtures, optical isomers, pharmaceutically-acceptable salts, prodrugs or biologically active metabolites thereof wherein:

G is 

where Z^{100} is  or a group optionally substituted with R_1 selected from the group consisting of alkyl, cycloalkyl, pyrrolidinyl, quinolinyl, quinoxalinyl, quinazolinyl, isoquinolinyl, phthalazinyl, imidazo[1,2-a]pyrimidinyl, 1H-imidazo[1,2-a]imidazolyl, imidazo[2,1-b][1,3]thiazolyl, naphthyl, tetrahydronaphthyl, benzothienyl, furanyl, thienyl, benzoxazolyl, benzoisoxazolyl, benzothiazolyl,  ,  ,



, thiazolyl, benzofuranyl, 2,3-dihydrobenzofuranyl, indolyl, isoxazolyl, tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, pyrazolyl, pyrrolyl, pyrrolopyridinyl, H-pyridinone, oxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, indolinyl, indazolyl, imidazo[1,2-a]pyridinyl, benzoisothiazolyl, 1,1-dioxybenzoisothiazolyl, pyrido-oxazolyl, pyrido-thiazolyl, pyrimido-oxazolyl, pyrimido-thiazolyl and benzimidazolyl;

Z^{110} is a covalent bond, or an optionally substituted (C_1-C_6) which is optionally substituted with one or more substituents selected from the group consisting of alkyl, CN, OH, halogen, NO_2, COOH, substituted or unsubstituted amino and substituted or unsubstituted phenyl;

Z^{111} is a covalent bond, an optionally substituted (C_1-C_6) or an optionally substituted -$(CH_2)_n$-cycloalkyl-$(CH_2)_n$-; where the optionally substituted groups are optionally substituted with one or more substituents selected from the group consisting of alkyl, CN, OH, halogen, NO_2, COOH, substituted or unsubstituted amino and substituted or unsubstituted phenyl;

R_a and R_1 each represent one or more substituents for each occurrence independently selected from the group consisting of hydrogen, halogen, -CN, -NO_2, -C(O)OH, -C(O)H, -OH, -C(O)O-alkyl, -C(O)O-aryl, -C(O)O-heteroaryl, -C(O)-alkyl, -C(O)-aryl, -C(O)-heteroaryl, substituted or unsubstituted carboxamido, tetrazolyl, trifluoromethylcarbonylamino, trifluoromethylsulfonamido, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryloxy, substituted or unsubstituted heteroaryloxy, substituted or unsubstituted heteroarylalkoxy, substituted or unsubstituted arylalkoxy, substituted or unsubstituted alkyl-$S(O)_p$-, substituted or unsubstituted alkyl-S-, substituted or unsubstituted aryl-$S(O)_p$-,

substituted or unsubstituted heteroaryl-$S(O)_p$-, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted alkynyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted amido groups, substituted or unsubstituted heteroarylthio, substituted or unsubstituted arylthio, $-Z^{105}-C(O)N(R)_2$, $-Z^{105}-N(R)-C(O)-Z^{200}$, $-Z^{105}-N(R)-S(O)_2-Z^{200}$, $-Z^{105}-N(R)-C(O)-N(R)-Z^{200}$, R_c and CH_2OR_c;

where R_c for each occurrence is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, $-CH_2-NR_dR_e$, $-W-(CH_2)_t-NR_dR_e$, $-W-(CH_2)_t-O$-alkyl, $-W-(CH_2)_t-S$-alkyl, or $-W-(CH_2)_t-OH$;

Z^{105} for each occurrence is independently a covalent bond or (C_1-C_6);

Z^{200} for each occurrence is independently a substituted or unsubstituted (C_1-C_6), substituted or unsubstituted phenyl or substituted or unsubstituted $-(C_1-C_6)$-phenyl;

R_d and R_e for each occurrence are independently H, alkyl, alkanoyl or SO_2-alkyl; or R_d, R_e and the nitrogen atom to which they are attached together form a five- or six-membered heterocyclic ring;

t for each occurrence is independently an integer from 2 to 6;

W for each occurrence is independently a direct bond or O, S, S(O), $S(O)_2$, or NR_f, wherein R_f for each occurrence is independently H or alkyl; or

R_1 is a substituted or unsubstituted carbocyclic or heterocyclic ring fused with ring 2;

R_3 for each occurrence is, independently, hydrogen, hydroxy, substituted or unsubstituted alkyl, substituted or unsubstituted -C(O)-alkyl, a substituted or unsubstituted -C(O)-aryl, or a substituted or unsubstituted –C(O)-heteroaryl or substituted or unsubstituted alkoxy;

A is $-(C_1-C_6)$ -, -O-; -S-; $-S(O)_p$-; -N(R)-; -N(C(O)OR)-; -N(C(O)R)-; $-N(SO_2R)$-; $-CH_2O$-; $-CH_2S$-; $-CH_2N(R)$-; -CH(NR)-; $-CH_2N(C(O)R)$)-; $-CH_2N(C(O)OR)$-; $-CH_2N(SO_2R)$-; -CH(NHR)-; -CH(NHC(O)R)-; $-CH(NHSO_2R)$-; -CH(NHC(O)OR)-; -CH(OC(O)R)-; -

$CH(OC(O)NHR)$-; -CH=CH-; -C(=NOR)-; -C(O)-; -CH(OR)-; -C(O)N(R)-; -N(R)C(O)-; -N(R)S(O)$_p$-; -OC(O)N(R)-; ; -N(R)-C(O)-$(CH_2)_n$-N(R)-, -N(R)C(O)O-; -N(R)-$(CH_2)_{n+1}$-C(O)-, -S(O)$_p$N(R)-; -O-$(CR_2)_{n+1}$-C(O)-, -O-$(CR_2)_{n+1}$-O-, -N(C(O)R)S(O)$_p$-; -N(R)S(O)$_p$N(R)-; -N(R)-C(O)-$(CH_2)_n$-O-, -C(O)N(R)C(O)-; -S(O)$_p$N(R)C(O)-; -OS(O)$_p$N(R)-; -N(R)S(O)$_p$O-; -N(R)S(O)$_p$C(O)-; -SO$_p$N(C(O)R)-; -N(R)SO$_p$N(R)-; -C(O)O-; -N(R)P(OR$_b$)O-; -N(R)P(OR$_b$)-; -N(R)P(O)(OR$_b$)O-; -N(R)P(O)(OR$_b$)-; -N(C(O)R)P(OR$_b$)O-; -N(C(O)R)P(OR$_b$)-; -N(C(O)R)P(O)(OR$_b$)O-, or -N(C(O)R)P(OR$_b$)-;

where R for each occurrence is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl or substituted or unsubstituted aryl;

R_b for each occurrence is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl or substituted or unsubstituted aryl;

p is 1 or 2; or

in a phosphorus containing group, the nitrogen atom, the phosphorus atom, R and R_b together form a five- or six-membered heterocyclic ring; or

A is $NRSO_2$ and R, R_a and the nitrogen atom together form a substituted or unsubstituted five or-six-membered heterocyclic ring fused to ring 1; or

Z^{110}-A-Z^{111} taken together is a covalent bond; and

R_2 is a group of the formula -Z^{101}-Z^{102};

Z^{101} is a covalent bond, -(C_1-C_6)-, -(C_1-C_6)- -O-, -(C_1-C_6)- -C(O)-, -(C_1-C_6)- -C(O)O-, -(C_1-C_6)-C(O)-NH-, -(C_1-C_6)-C(O)-N((C_1-C_6))- or a substituted or unsubstituted phenyl group;

Z^{102} is a substituted, saturated or unsaturated heterocyclic group; or a substituted, saturated or unsaturated heterobicyclic group; wherein said substituted heterocyclic and substituted heterobicyclic group have one or more substituents each independently selected from the group consisting of nitro, halo, substituted or unsubstituted (C_1-C_6), substituted or unsubstituted aryl, substituted or unsubstituted -C(O)-alkyl, substituted or unsubstituted -N(R)-(C_1-C_6) -OR, substituted or

unsubstituted –N((C_1-C_6) -OR)$_2$,substituted or unsubstituted -N(R)-(C_1-C_6) -C(O)$_2$R, substituted or unsubstituted –(C_1-C_6) -N(R)-(C_1-C_6) -OR, substituted or unsubstituted –(C_1-C_6) -N(R)-(C_1-C_6) -N(R)$_2$, substituted or unsubstituted –(C_1-C_6) -C(O)N(R)-(C_1-C_6) -N(R)$_2$, substituted or unsubstituted –N(R)-(C_1-C_6) -OR, and a substituted or unsubstituted heterocyclic group comprising one or more heteroatoms selected from the group consisting of O, and S; wherein the nitrogen atoms of said heterocyclic group or heterobicyclic group are independently optionally substituted by oxo, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted -C(O)N(R)$_2$, substituted or unsubstituted -C(O)-(C_1-C_6)-N(R)$_2$, -C(O)-alkyl, -C(O)-aryl, -C(O)-heteroaryl, substituted or unsubstituted arylalkyl group, or substituted or unsubstituted heteroarylalkyl;

a is 1 and D_1, G_1, J_1, L_1 and M_1 are each independently selected from the group consisting of CR_a and N, provided that at least two of D_1, G_1, J_1, L_1 and M_1 are CR_a; or

a is 0, and one of D_1, G_1, L_1 and M_1 is NR_a, one of D_1, G_1, L_1 and M_1 is CR_a and the remainder are independently selected from the group consisting of CR_a and N, wherein R_a is as defined above;

b is 1 and D_2, G_2, J_2, L_2 and M_2 are each independently selected from the group consisting of CR_a and N, provided that at least two of D_2, G_2, J_2, L_2 and M_2 are CR_a; or

b is 0, and one of D_2, G_2, L_2 and M_2 is NR_a, one of D_2, G_2, L_2 and M_2 is CR_a and the remainder are independently selected from the group consisting of CR_a and N, wherein R_a is as defined above; and

n for each occurrence is independently an integer from 0 to 6;

provided that when A is –N(R)-, Z^{110} and Z^{111} are each a covalent bond, and R_2 is a 3,4-diacyloxytetrahydrofur-2-yl, then Z^{100} is not alkyl, tetrahydropyranyl, tetrahydrofuranyl, piperidinyl or pyrrolidinyl;

provided that when Z^{110} and Z^{111} are each a covalent bond, and R_2 is a 3,4-diacyloxytetrahydrofur-2-yl, Z^{100} is a substituted or unsubstituted alkyl, then A is not alkyl, -O-, -C(O)-, -NHC(O)- or –C(O)O-;

provided that when Z^{110}-A-Z^{111} taken together are a covalent bond, then Z^{100} is not alkyl; and

provided that when Z^{110}-A-Z^{111} taken together are a C_1-C_6 alkyl, then Z^{100} is not phenyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, furyl or thienyl.

113. A method of inhibiting one or more protein kinase activity in a patient comprising administering a therapeutically effective amount of a compound of Claim 89, 101, 107, 108, 109, 110, 111 or 112 or a physiologically acceptable salt, prodrug or biologically active metabolites thereof to said patient.

114. The method of Claim 113 wherein said protein kinase is selected from the group consisting of KDR, FGFR-1, PDGFRβ, PDGFRα, IGF-1R, c-Met, Flt-1, Flt-4, TIE-2, TIE-1, Lck, Src, fyn, Lyn, Blk, hck, fgr and yes.

115. A method of affecting hyperproliferative disorders in a patient comprising administering a therapeutically effective amount of a compound of Claim 89, 101, 107, 108, 109, 110, 111 or 112 or a physiologically acceptable salt, prodrug or biologically active metabolites thereof to said patient.

116. A method of affecting angiogenesis in a patient comprising administering a therapeutically effective amount of a compound of Claim 89, 101, 107, 108, 109, 110, 111 or 112 or a physiologically acceptable salt, prodrug or biologically active metabolites thereof to said patient.

117. The method of Claim 113 wherein the protein kinase is a protein serine/threonine kinase or a protein tyrosine kinase.

118. A method of treating one or more ulcers in a patient comprising administering a therapeutically effective amount of a compound of Claim 89, 101, 107, 108, 109, 110, 111 or 112 or a physiologically acceptable salt, prodrug or biologically active metabolites thereof to said patient.

119. The method of Claim 118 wherein the ulcer or ulcers are caused by a bacterial or fungal infection; or the ulcer or ulcers are Mooren ulcers; or the ulcer or ulcers are a symptom of ulcerative colitis.

120. A method of treating a condition in a patient comprising administering a therapeutically effective amount of a compound of Claim 89, 101, 107, 108, 109, 110, 111 or 112 or a physiologically acceptable salt, prodrug or biologically active metabolites thereof to said patient, wherein said condition is an ocular condition, a cardiovascular condition, a cancer, Crow-Fukase (POEMS) syndrome, a diabetic condition, sickle cell anaemia, chronic inflammation, systemic lupus, glomerulonephritis, synovitis, inflammatory bowel disease, Crohn's disease, glomerulonephritis, rheumatoid arthritis, osteoarthritis, multiple sclerosis, graft rejection, Lyme disease, sepsis, von Hippel Lindau disease, pemphigoid, psoriasis, Paget's disease, polycystic kidney disease, fibrosis, sarcoidosis, cirrhosis, thyroiditis, hyperviscosity syndrome, Osler-Weber-Rendu disease, chronic occlusive pulmonary disease, asthma or edema following burns, trauma, radiation, stroke, hypoxia, ischemia, ovarian hyperstimulation syndrome, preeclampsia, menometrorrhagia, endometriosis, or infection by Herpes simplex, Herpes Zoster, human immunodeficiency virus, parapoxvirus, protozoa or toxoplasmosis.

121. The method of Claim 120 wherein the ocular condition is ocular or macular edema, ocular neovascular disease, scleritis, radial keratotomy, uveitis, vitritis, myopia, optic pits, chronic retinal detachment, post-laser treatment complications, conjunctivitis, Stargardt's disease, Eales disease, retinopathy or macular degeneration.

122. The method of Claim 120 wherein the cardiovascular condition is atherosclerosis, restenosis, ischemia/reperfusion injury, vascular occlusion or carotid obstructive disease.

123. The method of Claim 120 wherein the cancer is a solid tumor, a sarcoma, fibrosarcoma, osteoma, melanoma, retinoblastoma, a rhabdomyosarcoma, glioblastoma, neuroblastoma, teratocarcinoma, an hematopoietic malignancy, Kaposi's sarcoma, Hodgkin's disease, lymphoma, myeloma, leukemia or malignant ascites.

124. The method of Claim 120 wherein the diabetic condition is insulin-dependent diabetes mellitus glaucoma, diabetic retinopathy or microangiopathy.

125. A method of decreasing fertility in a patient, said method comprising the step of administering to the patient an effective amount of a compound of Claim 89, 101, 107, 108, 109, 110, 111 or 112 or a physiologically acceptable salt, prodrug or biologically active metabolite thereof.

126. The method of Claim 116 wherein the compound or a physiologically acceptable salt, prodrug or biologically active metabolite thereof is administered in an amount effective to promote angiogenesis or vasculogenesis.

127. The method of Claim 114 wherein the protein kinase is Tie-2.

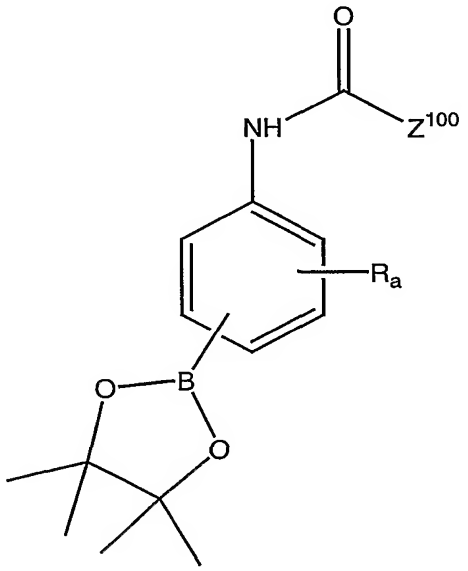
128. The method of Claim 126 wherein the compound of Formula I, or physiologically acceptable salt, prodrug or biologically active metabolite thereof, is administered in combination with a pro-angiogenic growth factor.

129. The method of Claim 128 wherein the pro-angiogenic growth factor is selected from the group consisiting of VEGF, VEGF-B, VEGF-C, VEGF-D, VEGF-E, HGF, FGF-1, FGF-2, derivatives thereof and antiiodotypic antibodies.

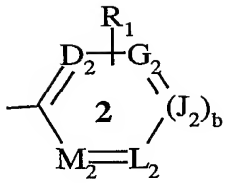
130. The method of Claim 126 wherein the patient is suffering from anemia, ischemia, infarct, transplant rejection, a wound, gangrene or necrosis.

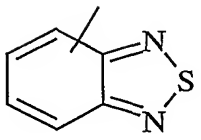
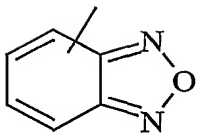
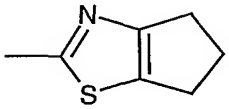
131. The method of Claim 113 wherein the protein kinase activity is involved in T cell activation, B cell activation, mast cell degranulation, monocyte activation, the potentiation of an inflammatory response or a combination thereof.

132. A method of preparing a 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl intermediate represented by the following structural formula:



wherein:

Z^{100} is  or a group optionally substituted with R_1 selected from the group consisting of alkyl, cycloalkyl, pyrrolidinyl, quinolinyl, quinoxalinyl, quinazolinyl, isoquinolinyl, phthalazinyl, imidazo[1,2-a]pyrimidinyl, 1H-imidazo[1,2-a]imidazolyl, imidazo[2,1-b][1,3]thiazolyl, naphthyl, tetrahydronaphthyl, benzothienyl, furanyl, thienyl, benzoxazolyl, benzoisoxazolyl,

benzothiazolyl,  ,  , 

, thiazolyl, benzofuranyl, 2,3-dihydrobenzofuranyl, indolyl, isoxazolyl, tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, pyrazolyl, pyrrolyl, pyrrolopyridinyl, H-pyridinone, oxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, indolinyl, indazolyl, imidazo[1,2-a]pyridinyl, benzoisothiazolyl, 1,1-dioxybenzoisothiazolyl, pyrido-oxazolyl, pyrido-thiazolyl, pyrimido-oxazolyl, pyrimido-thiazolyl and benzimidazolyl;

R_a and R_1 represent one or more substituents for each occurrence independently selected from the group consisting of hydrogen, halogen, -CN, -NO_2, -C(O)OH, -C(O)H, -OH, -C(O)O-alkyl, -C(O)O-aryl, -C(O)O-heteroaryl, -C(O)-alkyl, -C(O)-aryl, -C(O)-heteroaryl, substituted or unsubstituted carboxamido, tetrazolyl, trifluoromethylcarbonylamino, trifluoromethylsulfonamido, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryloxy, substituted or unsubstituted heteroaryloxy, substituted or unsubstituted heteroarylalkoxy, substituted or unsubstituted arylalkoxy, substituted or unsubstituted alkyl-$S(O)_p$-, substituted or unsubstituted alkyl-S-, substituted or unsubstituted aryl-$S(O)_p$-, substituted or unsubstituted heteroaryl-$S(O)_p$-, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted alkynyl, substituted or unsubstituted amino, substituted or unsubstituted aminoalkyl, substituted or unsubstituted amido groups, substituted or unsubstituted heteroarylthio, substituted or unsubstituted arylthio, -Z^{105}-C(O)N(R)$_2$, -Z^{105}-N(R)-C(O)-Z^{200}, -Z^{105}-N(R)-$S(O)_2$-Z^{200}, -Z^{105}-N(R)-C(O)-N(R)-Z^{200}, R_c and CH_2OR_c;

where R_c for each occurrence is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, $-CH_2-NR_dR_e$, $-W-(CH_2)_t-NR_dR_e$, $-W-(CH_2)_t-O$-alkyl, $-W-(CH_2)_t-S$-alkyl, or $-W-(CH_2)_t-OH$;

Z^{105} for each occurrence is independently a covalent bond or (C_1-C_6);

Z^{200} for each occurrence is independently a substituted or unsubstituted (C_1-C_6), substituted or unsubstituted phenyl or substituted or unsubstituted $-(C_1-C_6)$-phenyl;

R_d and R_e for each occurrence are independently H, alkyl, alkanoyl or SO_2-alkyl; or R_d, R_e and the nitrogen atom to which they are attached together form a five- or six-membered heterocyclic ring;

t for each occurrence is independently an integer from 2 to 6;

W for each occurrence is independently a direct bond or O, S, S(O), $S(O)_2$, or NR_f, wherein R_f for each occurrence is independently H or alkyl; or

R_1 is a substituted or unsubstituted carbocyclic or heterocyclic ring fused with ring 2; and

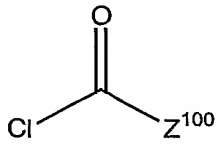
R for each occurrence is independently H, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl or substituted or unsubstituted aryl;

p is 1 or 2; and

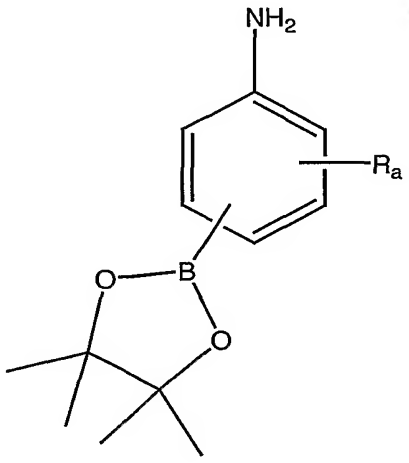
b is 1 and D_2, G_2, J_2, L_2 and M_2 are each independently selected from the group consisting of CR_a and N, provided that at least two of D_2, G_2, J_2, L_2 and M_2 are CR_a; or

b is 0, and one of D_2, G_2, L_2 and M_2 is NR_a, one of D_2, G_2, L_2 and M_2 is CR_a and the remainder are independently selected from the group consisting of CR_a and N, wherein R_a is as defined above;

comprising the step of reacting in the presence of an aprotic base an acid chloride represented by the following structural formula:

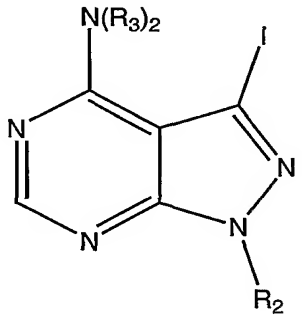


with a (4,4,5,5-tetramethyl-1,3,2-dioxaborolanyl)aniline represented by the following structural formula:



to form said 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl intermediate.

133. The method of Claim 132, further comprising the step of reacting the 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl intermediate in the presence of tetrakis(triphenylphosphine)palladium(0) and sodium carbonate with a 3-iodo-1*H*-pyrazolo[3,4-d]pyrimidine represented by the following structural formula:



wherein:

R_2 is H or a group of the formula $-Z^{101}-Z^{102}$;

Z^{101} is a covalent bond, $-(C_1-C_6)-$, $-(C_1-C_6)-O-$, $-(C_1-C_6)-C(O)-$, $-(C_1-C_6)-C(O)O-$, $-(C_1-C_6)-C(O)-NH-$, $-(C_1-C_6)-C(O)-N((C_1-C_6))-$ or a substituted or unsubstituted phenyl group;

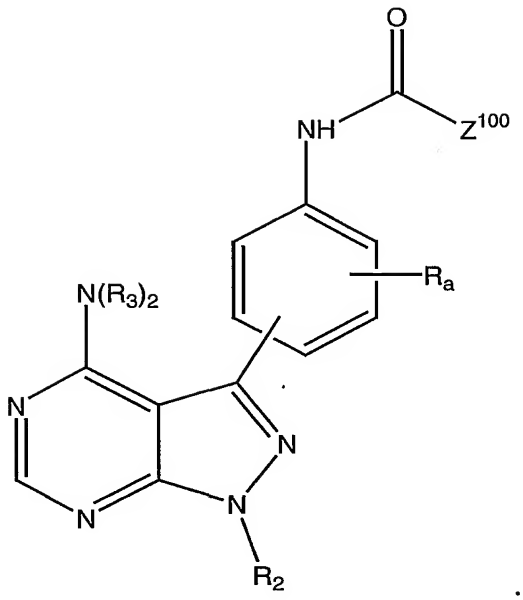
Z^{102} is hydrogen; a substituted or unsubstituted alkyl group; a substituted or unsubstituted cycloalkyl group; a substituted or unsubstituted cycloalkenyl, a substituted or unsubstituted, saturated or unsaturated heterocyclic group; or a substituted or unsubstituted, saturated or unsaturated heterobicyclic group; wherein said substituted alkyl, substituted cycloalkyl, substituted cycloalkenyl, substituted heterocyclic and substituted heterobicyclic group having one or more substituents each independently selected from the group consisting of hydroxyl, cyano, nitro, halo, substituted or unsubstituted (C_1-C_6), substituted or unsubstituted aryl, substituted or unsubstituted -C(O)-alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted -N(R)-(C_1-C_6) -OR, substituted or unsubstituted –N((C_1-C_6) -OR)$_2$,substituted or unsubstituted -N(R)-(C_1-C_6) -C(O)$_2$R, substituted or unsubstituted –(C_1-C_6) -N(R)-(C_1-C_6) -OR, substituted or unsubstituted –(C_1-C_6) -N(R)-(C_1-C_6) -N(R)$_2$, substituted or unsubstituted –(C_1-C_6) -C(O)N(R)-(C_1-C_6) -N(R)$_2$, substituted or unsubstituted sulfonamido, substituted or unsubstituted ureido, substituted or unsubstituted carboxamido, substituted or unsubstituted amino, substituted or unsubstituted –N(R)-(C_1-C_6) -OR, oxo, and a saturated, unsaturated or aromatic, substituted or unsubstituted heterocyclic group comprising one or more heteroatoms selected from the group consisting of N, O, and S; wherein the nitrogen atoms of said heterocyclic group or heterobicyclic group are independently optionally substituted by oxo, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted -C(O)N(R)$_2$, substituted or unsubstituted -C(O)-(C_1-C_6)-N(R)$_2$, -C(O)-alkyl, -C(O)-aryl, -C(O)-heteroaryl, substituted or unsubstituted arylalkyl group, or substituted or unsubstituted heteroarylalkyl; or

R_2 is a group of the formula -B-E, wherein B is a substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted azacycloalkyl, substituted or unsubstituted amino, substituted or unsubstituted

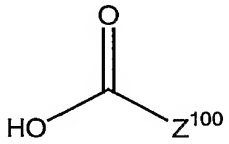
aminoalkylsulfonyl, substituted or unsubstituted alkoxyalkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aminoalkylcarbonyl, substituted or unsubstituted alkylene, substituted or unsubstituted aminoalkyl, substituted or unsubstituted alkylenecarbonyl or substituted or unsubstituted aminoalkylcarbonyl group; and E is substituted or unsubstituted alkyl, a substituted or unsubstituted cycloalkyl, substituted or unsubstituted azacycloalkyl, a substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted (C_1-C_6)-azacycloalkyl-, substituted or unsubstituted azacycloalkylcarbonyl, substituted or unsubstituted azacycloalkylsulfonyl, substituted or unsubstituted azacycloalkylalkyl, substituted or unsubstituted heteroaryl-N(R)-(C_1-C_6)-, substituted or unsubstituted aryl-N(R)-(C_1-C_6)-, substituted or unsubstituted alkyl-N(R)-(C_1-C_6)-, substituted or unsubstituted heteroaryl-(C_1-C_6)-N(R)-, substituted or unsubstituted aryl-(C_1-C_6)-N(R)-, substituted or unsubstituted alkyl-(C_1-C_6)-N(R)-, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroarylcarbonyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted arylcarbonyl, substituted or unsubstituted heteroarylsulfonyl, substituted or unsubstituted alkylsulfonyl, substituted or unsubstituted arylsulfonyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted azacycloalkylcarbonylamino, substituted or unsubstituted heteroarylcarbonylamino, substituted or unsubstituted arylcarbonylamino, substituted or unsubstituted alkylcarbonylamino or substituted or unsubstituted aryl; and

R_3 for each occurrence is, independently, hydrogen, hydroxy, substituted or unsubstituted alkyl, substituted or unsubstituted -C(O)-alkyl, a substituted or unsubstituted -C(O)-aryl, or a substituted or unsubstituted –C(O)-heteroaryl or substituted or unsubstituted alkoxy;

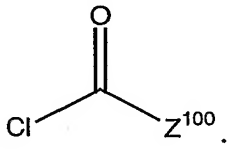
to form a compound represented by the following structural formula:



134. The method of Claim 133, further comprising the step of reacting a carboxylic acid represented by the following structural formula:



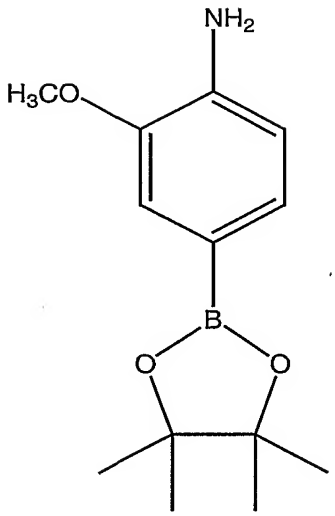
with oxalyl chloride and an aprotic base to form an acid chloride represented by the following structural formula:



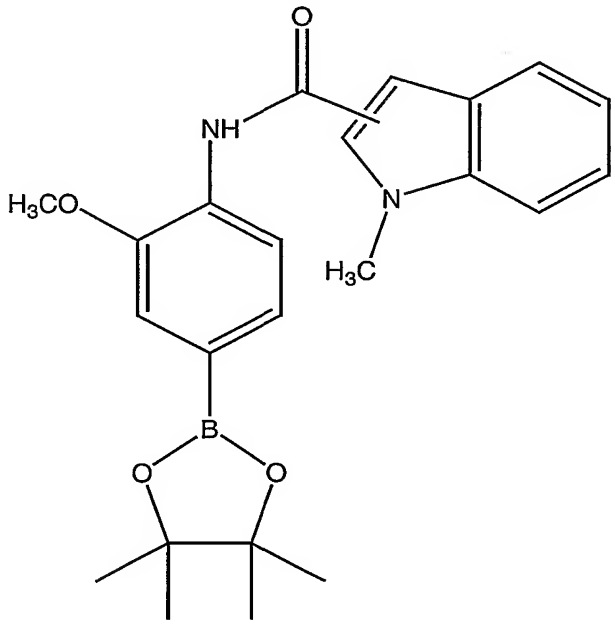
135. The method of Claim 132, 133 or 134 wherein Z^{100} is an indolyl which is optionally substituted with R_1.

136. The method of Claim 135, wherein Z^{100} is 1-methyl-indol-2-yl or 1-methyl-indol-3-yl.

137. The method of Claim 136, wherein the (4,4,5,5-tetramethyl-1,3,2-dioxaborolanyl)aniline is represented by the following structural formula:



and the 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl intermediate is represented by the following structural formula:



138. The method of Claim 137, wherein R_2 is 4-(4-methylpiperazino)cyclohexyl.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/09104

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 31/519; C07D 487/04
US CL : 544/262; 514/258.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 544/262; 514/258.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE, EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94/18215 A1 (GENSIA, INC.) 18 August 1994 (18.08.1994), page 7 of the specification or see claim 43.	1-138
A	US 5,646,128 A (FIRESTEIN ET AL) 8 July 1997 (08.07.1997), see column 18, lines 5-23.	1-138

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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"E" earlier application or patent published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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22 August 2002 (22.08.2002)

Date of mailing of the international search report
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